

PRODUCT MONOGRAPH
INCLUDING PATIENT MEDICATION INFORMATION

^NBELBUCA[®]

Buprenorphine Buccal Soluble Film

75 mcg, 150 mcg, 300 mcg, 450 mcg, 600 mcg, 750 mcg and 900 mcg of buprenorphine as buprenorphine hydrochloride.

Opioid Analgesic

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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Nonmedicinal Ingredients
Oral	Buccal soluble film Seven strengths with 75 mcg, 150 mcg, 300 mcg, 450 mcg, 600 mcg, 750 mcg and 900 mcg buprenorphine per film.	Carboxymethylcellulose sodium, citric acid anhydrous, hydroxypropylcellulose, hydroxyethylcellulose, methylparaben, monobasic sodium phosphate, peppermint oil, polycarbophil, propylene glycol, propylparaben, saccharin sodium, sodium benzoate, sodium hydroxide, titanium dioxide, vitamin E acetate, yellow iron oxide, purified water and black ink (Shellac, black iron oxide)

INDICATIONS AND CLINICAL USE

Adults:

BELBUCA[®] (buprenorphine buccal soluble film) is indicated for the management of pain severe enough to require daily, continuous, long-term treatment and:

- that is opioid-responsive; and
- for which alternative options are inadequate.

BELBUCA is not indicated as an as-needed (PRN) analgesic.

Geriatrics (> 65 years of age):

Clinical trials conducted with BELBUCA did not identify any notable differences in pharmacokinetics in subjects aged of > 65 compared to younger subjects. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, concomitant disease and other drug therapy. The dosage should be adjusted to the intensity of the pain and the sensitivity of the individual patient (see **ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions, Geriatrics**).

Pediatrics (< 18 years of age):

The safety and efficacy of BELBUCA have not been studied in the pediatric population. Therefore, use of BELBUCA is not indicated in patients under 18 years of age.

CONTRAINDICATIONS

BELBUCA® (buprenorphine buccal soluble film) is contraindicated in:

- Patients who are hypersensitive to the active substance (buprenorphine hydrochloride) or other opioid analgesics or to any ingredient in the formulation. For a complete listing, see the **DOSAGE FORMS, COMPOSITION AND PACKAGING** section of the Product Monograph.
- Patients with known or suspected oral mucositis
- Patients with mild pain
- Patients with intermittent or short duration pain
- The management of acute pain, including use in out-patient or day surgeries
- Patients with suspected surgical abdomen (e.g., acute appendicitis or pancreatitis)
- The management of peri-operative pain relief, or in other situations characterized by rapidly varying analgesic requirements
- Patients with acute asthma or other obstructive airway, and status asthmaticus
- Patients with acute respiratory depression, elevated carbon dioxide levels in the blood, and cor pulmonale
- Patients with acute alcoholism, or alcohol dependence, delirium tremens, and convulsive/seizure disorders
- Patients with severe CNS depression, increased cerebrospinal or intracranial pressure, and head injury
- Patients taking monoamine oxidase (MAO) inhibitors (or within 14 days of such therapy)
- Women who are pregnant, breast-feeding or during labour and delivery (see **SERIOUS WARNINGS AND PRECAUTIONS and WARNINGS AND PRECAUTIONS**)
- Opioid withdrawal and dependence substitution treatment
- Patients suffering from myasthenia gravis
- Patients with known or suspected mechanical gastrointestinal obstruction (e.g., bowel obstruction, strictures) or any diseases/conditions that affect bowel transit (e.g., ileus of any type)

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

Limitations of Use

Because of the risks of addiction, abuse, and misuse with opioids, even at recommended doses, which can lead to overdose and death, BELBUCA® should only be used in patients for whom alternative treatment options (e.g., non-opioid analgesics) are ineffective, not tolerated, or would be otherwise inadequate to provide sufficient management of pain (see DOSAGE AND ADMINISTRATION).

Addiction, Abuse, and Misuse:

BELBUCA poses risks of opioid addiction, abuse, and misuse, which can lead to overdose and death. Each patient's risk should be assessed prior to prescribing BELBUCA, and all patients should be monitored regularly for the development of these behaviors or conditions (see WARNINGS AND PRECAUTIONS). BELBUCA should be stored securely to avoid theft or misuse.

Life-threatening Respiratory Depression: OVERDOSE

Serious, life-threatening, or fatal respiratory depression may occur with use of BELBUCA. Infants exposed in-utero or through breast milk are at risk of life-threatening respiratory depression upon delivery or when nursed. Patients should be monitored for respiratory depression, especially during initiation of BELBUCA or following a dose increase. Misuse or abuse of BELBUCA by snorting or injecting buprenorphine extracted from BELBUCA film will result in the uncontrolled delivery of buprenorphine and pose a significant risk of overdose and death (see WARNINGS AND PRECAUTIONS). Further, instruct patients of the hazards related to taking opioids including fatal overdose.

Accidental Exposure:

Accidental consumption of even one dose of BELBUCA, especially by children, can result in a fatal overdose of buprenorphine (see DOSAGE AND ADMINISTRATION, Disposal, for instructions on proper disposal).

Neonatal Opioid Withdrawal Syndrome:

Prolonged maternal use of BELBUCA during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening (see WARNINGS AND PRECAUTIONS).

Interaction with Alcohol:

The co-ingestion of alcohol with BELBUCA should be avoided as it may result in dangerous addictive effects, causing serious injury or death (see WARNINGS AND PRECAUTIONS and DRUG INTERACTIONS).

Risks From Concomitant Use With Benzodiazepines Or Other CNS Depressants:

Concomitant use of opioids with benzodiazepines or other CNS depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death (see WARNINGS AND PRECAUTIONS, Neurologic and DRUG INTERACTIONS).

- Reserve concomitant prescribing of BELBUCA and benzodiazepines or other CNS depressants for use in patients for whom alternative treatment options are inadequate.
- Limit dosages and durations to the minimum required.
- Follow patients for signs and symptoms of respiratory depression and sedation.

General

Patients should be instructed not to give BELBUCA® (buprenorphine buccal soluble film) to anyone other than the patient for whom it was prescribed; as such inappropriate use may have severe medical consequences, including death. BELBUCA should be stored securely to avoid theft or misuse.

BELBUCA should ONLY be prescribed to patients who require continuous opioid treatment for pain management. Initiation doses higher than 75 mcg should not be used in opioid naïve patients (see DOSAGE AND ADMINISTRATION, Patients not receiving opioids at the time of initiation of BELBUCA treatment (opioid-naïve)).

BELBUCA should only be prescribed by persons knowledgeable in the continuous administration of potent opioids, in the management of patients receiving potent opioids for treatment of pain, and in the detection and management of respiratory depression, which includes the proper use of opioid receptor antagonists.

As with other CNS depressants, patients who have received BELBUCA should be monitored especially for signs of respiratory depression until a stable maintenance dose is reached.

BELBUCA film is intended for buccal use on intact oral mucosa only; use on areas of the mouth with any open sores or lesions can lead to an increase exposure to buprenorphine.

Patients should be cautioned not to consume alcohol while using BELBUCA as it may increase the chance of experiencing serious adverse events, including death.

Addiction, Abuse and Misuse:

There is a potential risk of abuse and misuse with BELBUCA, as with all opioids, which can lead to overdose and death. Therefore, BELBUCA should be prescribed and handled with caution. BELBUCA is intended for buccal mucosa use only. BELBUCA delivers the complete dose of buprenorphine when the film is fully dissolved in the mouth.

Patients should be assessed for their clinical risks for opioid abuse or addiction prior to being prescribed opioids. All patients receiving opioids should be routinely monitored for signs of misuse and abuse.

Opioids, such as BELBUCA, should be used with particular care in patients with a history of alcohol and illicit/prescription drug abuse. However, concerns about abuse, addiction, and diversion should not prevent the proper management of pain.

Opioids, such as BELBUCA, are sought by drug abusers and people with addiction disorders and are subject to criminal diversion. This risk should be considered when prescribing or dispensing BELBUCA in situations where the healthcare professional is concerned about increased risk of misuse, abuse or diversion.

Careful record keeping of prescribing information, including quantity, frequency, and renewal requests is strongly advised. Proper assessment of the patient, proper prescribing practices, periodic re-evaluation of therapy, and proper dispensing and storage are appropriate measures that help to limit misuse, abuse or diversion of opioid drugs.

Carcinogenesis and Mutagenesis

See Part II, TOXICOLOGY.

Cardiovascular

Hypotensive effects:

BELBUCA should be administered with caution to patients at risk for hypotension. Buprenorphine, like other opioids, may result in severe hypotension in patients whose ability to maintain adequate blood pressure is compromised by reduced blood volume or concurrent administration of drugs such as other opioids, antipsychotics (e.g. phenothiazines), sedative/hypnotics, tricyclic antidepressants, antihistamines, benzodiazepines, centrally-active anti-emetics, general anesthetics, diuretics, alpha and beta blockers, ACE inhibitors, angiotensin receptor blockers, calcium channel blockers, renin inhibitors, drugs for erectile dysfunction.

Patients receiving BELBUCA as their first around-the-clock opioid may be at increased risk of hypotension or orthostatic syncope, similar to that seen with other opioids. These patients should be monitored for signs of hypotension after initiating or titrating the dose of BELBUCA and dose adjustments may be needed.

QTc prolongation:

Buprenorphine products have been associated with QTc interval prolongation (see ACTION AND CLINICAL PHARMACOLOGY, Cardiac Electrophysiology). Cases of QTc interval prolongation have been observed in some subjects participating in BELBUCA clinical trials. Avoid the use of BELBUCA in patients with a history of Long QT Syndrome or an immediate family member with this condition or those taking Class IA antiarrhythmic medications (e.g., quinidine, procainamide, disopyramide), Class IC antiarrhythmic medications (e.g., flecainide, propafenone) or Class III antiarrhythmic medications (e.g. amiodarone).

QTc interval prolongation may lead to an increased risk of ventricular arrhythmias including torsade de pointes. Torsade de pointes is a polymorphic ventricular tachyarrhythmia. Generally, the risk of torsade de pointes increases with the magnitude of QTc interval prolongation produced by the drug. Torsade de pointes may be asymptomatic or experienced by the patient as dizziness, palpitations, syncope, or seizures. If sustained, torsade de pointes can progress to ventricular fibrillation and sudden cardiac death.

Particular care should be exercised when administering BELBUCA to patients who are suspected to be at an increased risk of experiencing torsade de pointes during treatment with drugs prolonging the QTc interval (see **DRUG INTERACTIONS**).

Risk factors for torsade de pointes in the general population include, but are not limited to, the following: female gender; age ≥ 65 years; baseline prolongation of the QT/QTc interval; presence of pathological genetic variants affecting cardiac ion channels or regulatory proteins, especially

congenital long QT syndromes; family history of sudden cardiac death at <50 years of age; cardiac disease (e.g., myocardial ischemia or infarction, congestive heart failure, cardiomyopathy, conduction system disease); history of arrhythmias; electrolyte disturbances (e.g., hypokalemia, hypomagnesemia, hypocalcemia) or conditions leading to electrolyte disturbances (e.g., persistent vomiting, eating disorders); bradycardia; acute neurological events (e.g., intracranial or subarachnoid haemorrhage, stroke, intracranial trauma); diabetes mellitus; and autonomic neuropathy.

When drugs that prolong the QTc interval are prescribed, healthcare professionals should counsel their patients concerning the nature and implications of the ECG changes, underlying diseases and disorders that are considered to represent risk factors, demonstrated and predicted drug-drug interactions, symptoms suggestive of arrhythmia, risk management strategies, and other information relevant to the use of the drug. Patients should be advised to contact their healthcare provider immediately to report any new chest pain or discomfort, changes in heartbeat, palpitations, dizziness, lightheadedness, fainting, or changes in or new use of other medications.

Concomitant Use of CYP3A4 Inhibitors

The concomitant use of BELBUCA with cytochrome P450 3A4 inhibitors may result in an increase in buprenorphine plasma concentrations, which could increase dose-related toxicity, including potential fatal respiratory depression. In this situation, special patient care and observation is appropriate (see **DRUG INTERACTIONS**).

Concomitant Use of CYP3A4 Inducers

The interaction between buprenorphine and CYP3A4 enzyme inducers has not been studied. Co-administration of BELBUCA and CYP3A4 enzyme inducers could lead to increased clearance which could lead to a decrease in buprenorphine plasma concentrations, lack of efficacy, or possibly, development of an abstinence syndrome in a patient who had developed physical dependence to buprenorphine. Dose adjustments should be considered until stable drug effects are achieved.

If co-administration of a CYP3A4 inducer is necessary while a patient is treated with BELBUCA, the patient should be monitored for signs of opioid withdrawal. Conversely, if the discontinuation of CYP3A4 inducers is necessary, the patient should be monitored for the emergence of adverse events (including potential fatal respiratory depression). In both cases, dose adjustments should be considered until stable drug effects are achieved (see **DRUG INTERACTIONS**).

Dependence/Tolerance

As with other opioids, tolerance and physical dependence may develop upon repeated administration of BELBUCA and there is a potential for development of psychological dependence.

Physical dependence and tolerance reflect the neuroadaptation of the opioid receptors to chronic exposure to an opioid, and are separate and distinct from abuse and addiction. Tolerance, as well as physical dependence, may develop upon repeated administration of opioids, and are not by themselves evidence of an addictive disorder or abuse. Buprenorphine is a partial μ -opioid agonist. Chronic use of buprenorphine can result in the development of a limited degree of physical dependence.

Patients on prolonged therapy should be tapered gradually from the drug if it is no longer required for pain control. Withdrawal symptoms may occur following abrupt discontinuation of therapy or upon administration of an opioid antagonist. Some of the symptoms that may be associated with abrupt withdrawal of an opioid analgesic include body aches, diarrhea, gooseflesh, loss of appetite, nausea, nervousness or restlessness, anxiety, runny nose, sneezing, tremors or shivering, stomach cramps, tachycardia, trouble with sleeping, unusual increase in sweating, palpitations, unexplained fever, weakness and yawning. Reports of physical dependence and withdrawal syndrome with buprenorphine treatment are uncommon.

BELBUCA should not be prescribed to patients with known physical dependence on other opioids. Due to its antagonist component, BELBUCA may not substitute for other opioids in such patients, as it may precipitate an abstinence syndrome depending on the level of physical dependence, and the timing and dose of buprenorphine. Caution should be exercised when prescribing BELBUCA to patients known to have, or suspected of having, problems with other drug or alcohol abuse or serious mental illness.

All buprenorphine products have some potential for opioid abuse and dependence. However, reports of abuse with BELBUCA in clinical trial were uncommon.

Use in Drug and Alcohol Addiction

BELBUCA has not been studied and is not approved for use in the management of addictive disorders. Its intended use in individuals with drug or alcohol dependence, either active or in remission, is for the management of pain requiring opioid analgesia. Patients with a history of addiction to drugs or alcohol may be at higher risk of becoming addicted to BELBUCA unless used under extreme caution and awareness.

Endocrine

Adrenal Insufficiency

Cases of adrenal insufficiency have been reported with opioid use, more often following greater than one month of use. Presentation of adrenal insufficiency may include non-specific symptoms and signs including nausea, vomiting, anorexia, fatigue, weakness, dizziness, and low blood pressure. If adrenal insufficiency is suspected, confirm the diagnosis with diagnostic testing as soon as possible. If adrenal insufficiency is diagnosed, treat with physiologic replacement doses of corticosteroids. Wean the patient off of the opioid to allow adrenal function to recover and continue corticosteroid treatment until adrenal function recovers. Other opioids may be tried as some cases reported use of a different opioid without recurrence of adrenal insufficiency. The information available does not identify any particular opioids as being more likely to be associated with adrenal insufficiency.

Gastrointestinal

Buprenorphine and other morphine-like opioids have been shown to decrease bowel motility. Buprenorphine may obscure the diagnosis or clinical course of patients with acute abdominal conditions. BELBUCA is contraindicated in patients with known or suspected gastrointestinal obstruction, including paralytic ileus. Avoid use of BELBUCA in patients with other gastrointestinal conditions (see **CONTRAINDICATIONS**).

Hepatic/Biliary/Pancreatic

Cases of cytolytic hepatitis and hepatitis with jaundice have been observed in patients receiving sublingual formulations of buprenorphine for the treatment of opioid dependence, both in clinical trials and in post-marketing adverse events reports. The spectrum of abnormalities ranges from transient asymptomatic elevations in hepatic transaminases to case reports of hepatic failure, hepatic necrosis, hepatorenal syndrome, and hepatic encephalopathy. In many cases, the presence of pre-existing liver enzyme abnormalities, infection with hepatitis B or hepatitis C virus, concomitant usage of other potentially hepatotoxic drugs, and ongoing injection drug abuse may have played a causative or contributory role. For patients at increased risk of hepatotoxicity (e.g., patient with a history of excessive alcohol intake, intravenous drug abuse or liver disease), obtain baseline liver enzyme levels and monitor these levels periodically during treatment with BELBUCA. Buprenorphine may cause spasm of the Sphincter of Oddi and may cause increase in the serum amylase concentration. Patients with biliary/pancreatic duct diseases should be monitored for worsening symptoms.

Immune

Allergic Reactions:

Cases of acute and chronic hypersensitivity to buprenorphine have been reported in clinical trials of buprenorphine marketed products. The most common signs and symptoms include rashes, hives and pruritus.

Cases of bronchospasm, angioneurotic edema, and anaphylactic shock have also been reported. A history of hypersensitivity to buprenorphine is a contraindication to BELBUCA use.

Neonatal Opioid Withdrawal Syndrome (NOWS)

Prolonged maternal use of opioids during pregnancy can result in withdrawal signs in the neonate. Neonatal opioid withdrawal syndrome, unlike opioid withdrawal syndrome in adults, may be life-threatening.

Neonatal opioid withdrawal syndrome presents as irritability, hyperactivity and abnormal sleep pattern, high pitched cry, tremor, vomiting, diarrhea and failure to gain weight. There have also been reports of convulsions, apnea, respiratory depression, and bradycardia. The onset, duration, and severity of neonatal opioid withdrawal syndrome vary based on the specific opioid used, duration of use, timing and amount of last maternal use as well as the rate of elimination of the drug by the newborn.

Use of BELBUCA is contraindicated in pregnant women (see **CONTRAINDICATIONS**).

In France, neonatal withdrawal has been reported in infants of women treated with sublingual buprenorphine for drug-addiction during pregnancy. Time to onset of withdrawal symptoms ranged from Day 1 to Day 8 of life with most occurring on Day 1 (69%). The most commonly-reported manifestations include abnormal crying, agitation, hypertonia, tremor and convulsions. Respiratory depression has occurred in neonates whose mothers had taken high doses, even for a short duration of time, in the third trimester.

Neurologic

Interactions with Central Nervous System Depressants (including benzodiazepines and alcohol): BELBUCA should be used with caution and in a reduced dosage during concomitant administration of other opioid analgesics, general anesthetics, sedative/hypnotics, tricyclic antidepressants, antipsychotics (e.g. phenothiazines), antihistamines, benzodiazepines, centrally-active anti-emetics and other CNS depressants. Respiratory depression, hypotension and profound sedation, coma or death may result. When such combination therapy is contemplated, a substantial reduction in the dose of one or both agents should be considered and patients should be carefully monitored. BELBUCA should not be consumed with alcohol as it may increase the chance of experiencing dangerous side effects, including death (see **DRUG INTERACTIONS**).

Observational studies have demonstrated that concomitant use of opioid analgesics and benzodiazepines increases the risk of drug-related mortality compared to use of opioid analgesics alone. Because of similar pharmacological properties, it is reasonable to expect similar risk with the concomitant use of other CNS depressant drugs with opioid analgesics (see **DRUG INTERACTIONS**). If the decision is made to prescribe a benzodiazepine or other CNS depressant concomitantly with an opioid analgesic, prescribe the lowest effective dosages and minimum durations of concomitant use. In patients already receiving an opioid analgesic, prescribe a lower initial dose of the benzodiazepine or other CNS depressant than indicated in the absence of an opioid, and titrate based on clinical response. If an opioid analgesic is initiated in a patient already taking a benzodiazepine or other CNS depressant, prescribe a lower initial dose of the opioid analgesic, and titrate based on clinical response. Follow patients closely for signs and symptoms of respiratory depression and sedation.

Advise both patients and caregivers about the risks of respiratory depression and sedation when BELBUCA is used with benzodiazepines or other CNS depressants (including alcohol and illicit drugs). Advise patients not to drive or operate heavy machinery until the effects of concomitant use of the benzodiazepine or other CNS depressant have been determined. Screen patients for risk of substance use disorders, including opioid abuse and misuse, and warn them of the risk for overdose and death associated with the use of additional CNS depressants including alcohol and illicit drugs (see **DRUG INTERACTIONS**).

BELBUCA should not be consumed with alcohol as it may increase the chance of experiencing dangerous side effects, including death (see **CONTRAINDICATIONS** and **ADVERSE REACTIONS**, Sedation, and **DRUG INTERACTIONS**).

Severe pain antagonizes the subjective and respiratory depressant actions of opioid analgesics. Should pain suddenly subside, these effects may rapidly become manifest.

Head Injury and Increased Intracranial Pressure: BELBUCA should not be used in patients who may be particularly susceptible to the intracranial effects of CO₂ retention such as those with evidence of increased intracranial pressure, impaired consciousness, shock, or coma. Respiratory depression may be exacerbated in the presence of head injury, intracranial lesions (e.g., space occupying tumours) or increased intracranial pressure. Pupillary responses and effects on consciousness resulting from buprenorphine may mask neurologic signs of increasing intracranial pressure. Opioids may obscure the clinical course of patients with head injury.

Convulsive or Seizure Disorders: BELBUCA is contraindicated in patients with active convulsive or seizure disorders as buprenorphine may aggravate convulsions in patients with convulsive disorders, and may induce or aggravate seizures in some clinical settings. In patients with a history of convulsive or seizures disorders, physicians may decide to prescribe BELBUCA. In those cases, the patient should be closely monitored during treatment.

Serotonin syndrome: BELBUCA could cause a rare but potentially life-threatening condition resulting from concomitant administration of serotonergic drugs (e.g. anti-depressants, migraine medications). Treatment with the serotonergic drug should be discontinued if such events (characterized by clusters of symptoms such as hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, mental status changes including confusion, irritability, extreme agitation progressing to delirium and coma) occur and supportive symptomatic treatment should be initiated. BELBUCA should not be used in combination with MAO inhibitors or serotonin-precursors (such as L-tryptophan, oxitriptan) and should be used with caution in combination with other serotonergic drugs (triptans, certain tricyclic antidepressants, lithium, tramadol, St. John's Wort) due to the risk of serotonergic syndrome (see **DRUG INTERACTIONS**).

Peri-Operative Considerations

BELBUCA is contraindicated for peri-operative pain relief, or in other situations characterized by rapidly varying analgesic requirements. In the case of planned chordotomy or other pain-relieving operations, patients should not be treated with BELBUCA for at least 48 hours before the operation and BELBUCA should not be used in the immediate post-operative period. Thereafter, if BELBUCA is to be continued after the patient recovers from the post-operative period, a new dosage should be administered in accordance with the changed need for pain relief. The risk of withdrawal in opioid-tolerant patients should be addressed as clinically indicated.

The administration of analgesics in the peri-operative period should be managed by healthcare providers with adequate training and experience (e.g., by an anesthesiologist) (see **CONTRAINDICATIONS**).

Psychomotor Impairment

Opioid analgesics, including buprenorphine, can have a depressant effect on mental and/or physical responses. Caution must be exercised in activities requiring mental alertness such as driving a car or operating heavy machinery, especially when BELBUCA doses are being adjusted or when other CNS active drugs are being added to the treatment regimen. This impairment may be potentiated by concomitant depressant medications such as other opioids, alcohol, antipsychotics (e.g. phenothiazines), sedatives/hypnotics, tricyclic antidepressants,

antihistamines, benzodiazepines, centrally-active anti-emetics or other CNS depressants. Patients using BELBUCA should not drive or operate dangerous machinery unless they are accustomed to the effects of the drug.

Respiratory

Life-threatening respiratory depression:

Serious, life-threatening, or fatal respiratory depression has been reported with the use of opioids, even when used as recommended. Respiratory depression from opioid use, if not immediately recognized and treated, may lead to respiratory arrest and death. Management of respiratory depression may include close observation, supportive measures, and use of opioid antagonists such as naloxone, depending on the patient's clinical status. Carbon dioxide (CO₂) retention from opioid-induced respiratory depression can exacerbate the sedating effects of opioids. Buprenorphine should be used with extreme caution in patients with substantially decreased respiratory reserve, pre-existing respiratory depression, hypoxia or hypercapnia (see **CONTRAINDICATIONS**).

While serious, life-threatening, or fatal respiratory depression can occur at any time during the use of BELBUCA, the risk is greatest during the initiation of therapy or following a dose increase. Closely monitor patients for respiratory depression when initiating therapy with BELBUCA and following dose increases.

Life-threatening respiratory depression is more likely to occur in the elderly, cachectic, or debilitated patients because they may have altered pharmacokinetics or altered clearance compared to younger, healthier patients (see **WARNINGS AND PRECAUTIONS, Special Populations**).

To reduce the risk of respiratory depression, proper dosing and titration of BELBUCA are essential. Overestimating the BELBUCA dose when converting patients from another opioid product can result in a fatal overdose with the first dose administered (see **DOSAGE AND ADMINISTRATION**).

IN CASE OF OVERDOSE, THE PRIMARY ACTION SHOULD BE TO RE-ESTABLISH ADEQUATE VENTILATION WITH MECHANICAL ASSISTANCE OF RESPIRATION, IF REQUIRED. THE ONSET OF ACTION OF NALOXONE MAY BE POSTPONED BY 30 MINUTES WHICH WILL DELAY ITS EFFECTIVENESS IN REVERSING RESPIRATORY DEPRESSION DURING THIS PERIOD OF TIME (see OVERDOSAGE).

Although BELBUCA is a partial opioid agonist, buprenorphine may cause hypoventilation at analgesic doses, especially in patients who have an underlying pulmonary condition or who receive other opioids or other CNS drugs associated with hypoventilation in addition to BELBUCA (see **DRUG INTERACTIONS** regarding the use of concomitant CNS active drugs).

In patients with respiratory depression, symptomatic treatment following standard intensive care measures should be instituted (see **OVERDOSAGE**).

Use in Patients with Chronic Pulmonary Disease:

Buprenorphine should be used with caution in patients with chronic pulmonary disease, cor pulmonale, decreased respiratory reserve and potentially compromised respiration. Normal analgesic doses of opioids may further decrease respiratory drive in these patients to the point of respiratory failure (see **CONTRAINDICATIONS**).

Skin

Oral Mucositis

Buprenorphine is absorbed more rapidly and to a greater extent in subjects with oral mucositis. BELBUCA is contraindicated in patients with known or suspected oral mucositis. If BELBUCA is used inadvertently, patients should be closely monitored for signs and symptoms of toxicity or overdose caused by increased levels of buprenorphine.

Patient Counselling Information

A patient information sheet is included in the package of BELBUCA[®] buccal soluble films dispensed to the patient.

Patients receiving BELBUCA should be given the following instructions by the physician:

1. Patients should be advised to never give BELBUCA to anyone other than the individual for whom it was prescribed as accidental ingestion or use by individuals (including children) other than the patient for whom it was originally prescribed, may lead to severe, even fatal, consequences. 2. Patients should be advised not to apply the BELBUCA film if they suffer from oral mucositis, a painful ulceration of the inside of the cheek.

3. Patients should be advised that BELBUCA must be applied immediately upon removal from the sealed package (pouch).

Additionally, patients should be advised of the following:

- Belbuca film should not be used if the pouch seal is broken, or if it is altered, cut or damaged in any way prior to application. The buccal film should be applied with a clean and dry finger and should be pressed and held in place into the inside of the wet cheek for 5 seconds to make sure the contact is complete.
- Eating and drinking any liquid must be avoided until the buccal film is completely dissolved (usually within 30 minutes). Drinking any liquid, including alcohol, before the buccal film is completely dissolved will decrease the absorption of buprenorphine and hence, efficacy.
- Belbuca film should not be applied to areas of the mouth with any open sores or lesions.

4. Patients should be advised to take BELBUCA as directed. The dose of BELBUCA should not be adjusted without consulting with a physician.

5. Patients should be advised that BELBUCA buccal films contain buprenorphine, an opioid pain medicine with a potential for abuse.

6. Patients should be advised that BELBUCA may impair mental and/or physical ability required for the performance of potentially hazardous tasks (e.g., driving, operating machinery).
7. Patients should be advised to not combine BELBUCA with alcohol or other centrally acting agents, such as other opioids, sleep medications (sedatives/hypnotics), antipsychotics, antidepressants, antihistamines, benzodiazepines, centrally-active anti-emetics unless it is advised by their physician because dangerous additive effects may occur, resulting in serious injury or death.
8. Patients should be advised to consult their physician or pharmacist if other medications are being, or will be, used with BELBUCA.
9. Patients should be advised that when cessation of therapy is indicated, it is appropriate to taper the BELBUCA dose, rather than abruptly discontinue it, due to the risk of precipitating withdrawal symptoms.
10. Patients, family members and caregivers should be advised to protect BELBUCA from theft or misuse in the work or home environment.
11. Patients should be instructed to keep BELBUCA in a secure place out of sight and reach of children due to the risk of fatal respiratory depression.
12. Women of childbearing potential who become or are planning to become pregnant should be advised to consult a physician prior to initiating or continuing therapy with BELBUCA.

Sexual Function/Reproduction

Long-term use of opioids may be associated with decreased sex hormone levels and symptoms such as low libido, erectile dysfunction, or infertility (see **ADVERSE REACTIONS, Post-Market Adverse Drug Reactions**).

Special Populations

Special Risk Groups: Use of BELBUCA, like all opioid analgesics, is associated with increased risk of harms and should be used carefully in patients with: severely impaired pulmonary function; adrenocortical insufficiency (e.g., Addison's disease); CNS depression or coma; toxic psychosis; high-risk debilitated patients; myxedema or hypothyroidism; prostatic hypertrophy or urethral stricture; and in debilitated patients. Reduced dosage is advised in these conditions.

Buprenorphine is contraindicated in patients with acute alcoholism/alcohol dependence (see **CONTRAINDICATIONS**) and should be administered with caution to patients with a history of alcohol and drug abuse.

Pregnant Women: There are no adequate and well-controlled studies in pregnant women. Buprenorphine crosses the placental barrier and has been detected in newborn blood, urine and meconium. BELBUCA is contraindicated in pregnant women (see **CONTRAINDICATIONS**).

Prolonged maternal use of opioids during pregnancy can result in withdrawal signs in the neonate. Neonatal opioid withdrawal syndrome, unlike opioid withdrawal syndrome in adults, may be life-threatening (see **WARNINGS AND PRECAUTIONS, Neonatal Opioid Withdrawal Syndrome**).

Labour, Delivery and Nursing Women: BELBUCA is contraindicated during labour, delivery, pregnancy and in nursing mothers (see **CONTRAINDICATIONS**). Buprenorphine can cross the placental barrier and is also excreted in breast milk. Life-threatening respiratory depression may occur in the infant if opioids are administered to the mother. Naloxone, a drug that counters the effects of opioids should be readily available if BELBUCA is used in this population.

Pediatrics (< 18 years of age): The safety and efficacy of BELBUCA have not been studied in the pediatric population. Therefore, use of BELBUCA is not recommended in patients under 18 years of age.

Geriatrics (> 65 years of age): Of the total number of patients in the clinical trials (1889), BELBUCA was administered to 290 patients aged 65 years and older. Of those, 29 patients were aged 75 years and older. The incidences of selected BELBUCA-related adverse effects were higher in older subjects.

In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range and titrate slowly, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

Patient with Renal Impairment: No studies in patients with renal impairment have been performed with BELBUCA. In an independent study, the effect of impaired renal function on buprenorphine pharmacokinetics after IV administration was evaluated; and no notable differences in plasma buprenorphine concentrations were identified in patients with normal renal function compared to patients with impaired or renal failure. Therefore, no special dose adjustment of buprenorphine is necessary in patients with renal impairment.

Patient with Hepatic Impairment: BELBUCA has not been evaluated in patients with moderate and severe hepatic impairment. The effects of hepatic impairment on the pharmacokinetics of buprenorphine were evaluated in a pharmacokinetic study. Buprenorphine is extensively metabolized in the liver and buprenorphine plasma levels were found to be higher, and the half-life was found to be longer, in subjects with moderate and severe hepatic impairment, but not in subjects with mild hepatic impairment. For patients with severe hepatic impairment, a dose adjustment is recommended. Patients with moderate or severe hepatic impairment should be monitored for signs and symptoms of toxicity or overdose caused by increased levels of buprenorphine.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

Serious adverse drug reactions which may be associated with BELBUCA[®] (buprenorphine buccal soluble film) therapy in clinical use are those observed with other opioid analgesics, including respiratory depression (especially when used with other CNS depressants) and hypotension. Care must be exercised when using BELBUCA in patients who are using benzodiazepines or other agents with CNS activity.

The adverse drug reactions seen on initiation of therapy with BELBUCA in clinical studies are those often observed with other opioid analgesics (nausea, vomiting, constipation, dry mouth, dizziness, somnolence, pruritus). The frequency of these events depends on the dose, the clinical setting, the patient's level of opioid tolerance, and factors specific to the individual. They should be expected and managed as part of opioid analgesic therapy.

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

The safety of BELBUCA has been evaluated in five (5) Phase 3 studies comprised of 3 efficacy studies (12-week randomized double-blind, placebo controlled trials including an open-label titration period) and 2 long-term open-label trials conducted in patients with chronic pain. A total of 2,127 patients were treated with BELBUCA in the controlled and open-label clinical trials. There were 504 patients treated for approximately six months and 235 patients treated for approximately one year. The most common adverse events ($\geq 2\%$) leading to discontinuation was nausea, vomiting and liver function test abnormality.

For the pivotal study EN3409-308 in opioid-naïve patients, 61% of the patients who entered the **open-label dose titration period** were able to titrate to a tolerable and effective dose. During the open-label dose titration period, 15% of patients discontinued due to an adverse event and 4% discontinued due to lack of efficacy; a remaining 20% of patient discontinued due to various administrative reasons. During the **double-blind period**, of the 230 patients randomized to BELBUCA, 5.7% discontinued due to adverse events and 3.5% due lack of efficacy. Of the 232 patients randomized to placebo, 9.9% discontinued due to lack of efficacy and 3.0% due to adverse events.

For the pivotal study EN3409-307 in opioid-experienced patients, 63% of the patients who entered the **open-label titration period** were able to titrate to a tolerable and effective dose. During the open-label dose titration period, 10% of patients discontinued due to an adverse event, 8% discontinued due to lack of efficacy and 0.1% discontinued due to opioid withdrawal; a remaining 20% of patients discontinued due to various administrative reasons. During the **double-blind period**, of the 254 patients randomized to BELBUCA, 7.5% discontinued due to lack of efficacy, 2% due to adverse events and 0.4% discontinued due to opioid withdrawal. Of

the 257 patients randomized to placebo, 23.7% discontinued due to lack of efficacy, 5.1% due to adverse events and 3.5% discontinued due to opioid withdrawal.

Tables 1 and 2 list the treatment-emergent adverse events, regardless of causality, reported by at least 3% of subjects who received BELBUCA during the double-blind treatment period in 2 placebo-controlled 12-week trials in **opioid naïve (Table 1) and opioid experienced (Table 2)** subjects with moderate to severe chronic low back pain (CLBP).

Table 1: Treatment-emergent adverse events reported in $\geq 3\%$ of subjects and at a greater incidence than placebo during the double-blind treatment period in the 12-week controlled study (EN3409-308) in opioid naïve subjects with moderate-to-severe CLBP

System Organ Class Preferred term	Open-label Titration Phase	Double-blind Treatment Phase			
	Belbuca (N=749) %	Belbuca (N= 229)			Placebo (N=232) %
		150 mcg (N=58) %	300 mcg (N=67) %	450 mcg (N=104) %	
Gastrointestinal Disorders					
Nausea	49.8	13.8	10.4	7.7	7.3
Constipation	13.0	--	6.0	4.8	2.6
Vomiting	7.7	3.4	7.5	1.9	0.4
Nervous System Disorders					
Somnolence	6.9	--	3.0	--	0.4
Infections and infestations					
Urinary tract infection	2.0	--	3.0	1.0	2.2
Musculoskeletal and connective tissue disorders					
Myalgia	0.4	--	3.0	--	0.4
Respiratory, thoracic and mediastinal disorders					
Pulmonary Congestion	0.1	3.4	--	--	--
Cardiac disorders					
Atrial fibrillation	--	--	3.0	--	--
The following treatment-emergent adverse events were reported at a rate between 1 and 3 % and at a greater incidence than placebo during the double-blind treatment phase of this study: dry mouth, abdominal pain upper, toothache, diverticulum intestinal, rectal haemorrhage, small intestinal obstruction, dyspepsia, colitis, gastric ulcer, gastritis, abdominal pain, dental caries, dizziness, tremor, tooth infection, sinusitis, cellulitis, ear infection, folliculitis, postoperative wound infection, bronchitis, nasopharyngitis, hordeolum, cervicitis, gingival abscess, gastroenteritis viral, influenza, alanine aminotransferase increase, blood glucose increased, protein urine present, urinary casts, urine leukocyte esterase positive, weight decreased, white blood cell count increased, gamma-glutamyltransferase increased, blood alkaline phosphatase increased, aspartate aminotransferase increased, blood phosphorus increased, liver function test abnormal, pruritus, hyperhidrosis, dermal cyst, dermatitis contact, ingrown hair, rash vascular, acne, skin plaque, anxiety, insomnia, depression, muscle twitching, osteoarthritis, pain in jaw, musculoskeletal pain, bone pain, musculoskeletal stiffness, rotator cuff syndrome, pain in extremity, arthropod sting, meniscus injury, contusion, fall, laceration, epicondylitis, procedural headache, thermal burn, gingival injury, muscle strain, rib fracture, rhinorrhea, dysphonia, epistaxis, decreased appetite, dehydration, hyperslycaemia, diabetes mellitus, hypercholesterolaemia, hyperlipidaemia, hypokalaemia, hypertriglyceridaemia, anaemia, hypertension, nephrolithiasis, ear pain, menopausal symptoms, dysmenorrhoea, seasonal allergy, dysgeusia, cough.					

Table 2: Treatment-emergent adverse events reported in $\geq 3\%$ of subjects and at a greater incidence than placebo during the double-blind treatment period in the 12-week controlled study (EN3409-307) in opioid experienced subjects with moderate-to-severe CLBP

System Organ Class Preferred term	Open-label Titration Phase	Double-blind Treatment Phase					
	Belbuca	Belbuca (N= 254)					Placebo
	(N=810) %	300 mcg (N=30) %	450 mcg (N=36) %	600 mcg (N=43) %	750 mcg (N=42) %	900 mcg (N=93) %	Placebo (N=256) %
Gastrointestinal Disorders							
Vomiting	6.7	3.3	--	2.3	4.8	8.6	2.3
Nausea	16.8	13.3	--	7.0	7.1	7.5	7.4
Constipation	8.3	--	2.8	--	2.4	5.4	0.8
Abdominal pain	0.9	3.3	--	--	--	1.1	1.6
Lip blister	--	3.3	--	--	--	1.1	--
Abdominal pain lower	--	--	--	--	4.8	--	--
Gastroesophageal reflux disease	0.7	3.3	--	--	--	--	0.4
Nervous System Disorders							
Migraine	0.5	3.3	2.8	2.3	--	--	0.4
Infections and infestations							
Nasopharyngitis	2.3	--	--	--	2.4	4.3	2.0
Gastroenteritis viral	0.6	3.3	--	2.3	--	3.2	0.8
Urinary tract infection	2.8	6.7	8.3	2.3	--	2.2	0.8
Upper respiratory tract infection	2.2	6.7	8.3	--	--	2.2	2.3
Sinusitis	1.0	3.3	8.3	2.3	2.4	1.1	1.2
Gastroenteritis	0.2	3.3	2.8	--	2.4	--	0.8
Viral infection	0.2	--	--	4.7	--	--	--
Bronchitis	0.7	3.3	--	2.3	--	--	0.8
Infected skin ulcer	0.1	3.3	--	2.3	--	--	--
General Disorders and Administration Site Conditions							
Oedema peripheral	2.1	3.3	--	--	2.4	1.1	0.8
Musculoskeletal and Connective Tissue Disorders							
Back pain	1.6	--	2.8	2.3	--	5.4	0.4
Arthralgia	1.0	3.3	--	--	2.4	1.1	0.8
Injury, poisoning and procedural complications							
Fall	1.6	3.3	--	2.3	--	4.3	1.2
Synovial rupture	--	3.3	--	--	--	--	--
Vascular disorders							
Hypertension	1.5	3.3	--	2.3	--	1.1	--
Hot flushing	1.4	3.3	--	2.3	2.4	--	1.6
Haematoma	0.2	3.3	--	--	2.4	--	--
Metabolism and nutrition disorders							
Gout	0.2	--	--	--	4.8	--	0.4

System Organ Class Preferred term	Open-label Titration Phase	Double-blind Treatment Phase					
	Belbuca	Belbuca (N= 254)					Placebo
	(N=810) %	300 mcg (N=30) %	450 mcg (N=36) %	600 mcg (N=43) %	750 mcg (N=42) %	900 mcg (N=93) %	Placebo (N=256) %
Investigations							
Blood testosterone decrease	0.2	3.3	2.8	--	2.4	1.1	0.8
Creatinine renal clearance decreased	0.4	3.3	--	--	--	--	--
Reproductive system and breast disorders							
Menopausal symptoms	--	3.3	--	--	--	--	--
Blood and lymphatic system disorders							
Anaemia	0.2	--	--	--	4.8	--	--
<p>The following treatment-emergent adverse events were reported at a rate between 1 and 3 % and at a greater incidence than placebo during the double-blind treatment phase of this study : stomatitis, toothache, diverticulum, lip swelling, sensitivity of teeth, gingival cyst, hiatus hernia, dental caries, restless legs syndrome, influenza, pharyngitis streptococcal, acute sinusitis, tooth abscess, kidney infection, oesophageal candidiasis, otitis media, fatigue, pyrexia, pain, influenza like illness, irritability, cyst, inflammation, hyperhidrosis, pruritus (generalized), swelling face, dermatitis, acne, dermatitis contact, muscle twitching, myalgia, osteoarthritis, neck pain, synovial cyst, tendonitis, musculoskeletal stiffness, insomnia, anorgasmia, abnormal dreams, nasal congestion, chronic obstructive pulmonary disease, cough, pulmonary congestion, dyspnea, wheezing, excoriation, muscle strain, arthropod bit, ligament sprain, ankle/foot fracture, cartilage injury, laceration, limb injury, thermal burn, hand fracture, anthropod sting, joint injury, pulmonary contusion, rib fracture, fibula fracture, tibia fracture, hypokalaemia, gamma-glutamyltransferase increased, electrocardiogram QT prolonged, blood phosphorus increase, weight increased, electrocardiogram abnormal, seasonal allergy, endometrial hyperplasia, testicular pain, hepatic steatosis, cholecystitis, hypogonadism, hypothyroidism, nephrolithiasis, bladder prolapse, bundle branch block left, dizziness, cellulitis, oropharyngeal pain, asthma, tooth fracture.</p>							

Less Common Clinical Trial Adverse Drug Reactions (<1%)

The following adverse events were reported at a frequency of <1% with a possible causal relationship between these events and treatment with BELBUCA in either the open-label titration phase or double-blind treatment phases of the safety and efficacy studies.

Blood and Lymphatic System Disorders: Lymphadenopathy, thrombocytopenia.

Cardiovascular: Angina pectoris, atrial fibrillation, bradycardia, bundle branch block right, palpitations, tachycardia.

Ear and Labyrinth Disorders: Tinnitus, vertigo.

Endocrine Disorders: Androgen deficiency, hypogonadism.

Eye Disorders: Blepharitis, conjunctivitis allergic, dry eye, eye discharge, eye haemorrhage, eye pruritus, lacrimation increased, vision blurred, visual acuity reduced, visual impairment.

Gastrointestinal disorders: Abdominal discomfort, abdominal distension, abdominal pain, abdominal pain upper, abdominal pain lower, dyspepsia, eructation, faeces hard, flatulence, frequent bowel movements, gastrointestinal disorder, gastro-oesophageal reflux disease, glossodynia, hematochezia, hypoaesthesia oral, hyperchlorhydria, ileus, mouth ulceration, oedema mouth, oral disorder, paraesthesia oral, retching, salivary hypersecretion, stomatitis, toothache.

General Disorders and Administration Site Conditions: Application site anaesthesia, application site irritation, asthenia, chills, drug intolerance, drug withdrawal syndrome, feeling abnormal, feeling cold, feeling of body temperature change, feeling drunk, feeling hot, feeling jittery, hyperthermia, influenza like illness, irritability, malaise, nodule, product taste abnormal, pyrexia, sluggishness.

Hepatobiliary Disorders: Hyperbilirubinaemia.

Immune System Disorders: Hypersensitivity.

Infections and infestations: Candidiasis, cellulitis, mastoiditis, pharyngitis.

Injury, Poisoning and Procedural Complications: Accidental overdose, excoriation, upper limb fracture.

Investigations: Alanine aminotransferase increased, aspartate aminotransferase increased, blood alkaline phosphatase increased, blood creatine increased, blood pressure increased, blood phosphorus increased, blood testosterone free decreased, blood urea increased, blood uric acid increase, creatinine renal clearance decreased, electrocardiogram QT prolonged, gamma-glutamyltransferase increased, haematocrit decreased, haemoglobin decreased, hepatic enzyme increased, liver function test abnormal, platelet count decreased, platelet count increased, urine output decreased, weight decreased, weight increased.

Metabolism and Nutrition Disorders: Abnormal loss of weight, dehydration, diabetes mellitus, increased appetite.

Musculoskeletal and Connective Tissue Disorders: Arthralgia, back pain, bone pain, muscular weakness, myalgia, pain in extremity, joint swelling, muscle twitching, neck pain, osteoarthritis.

Nervous System Disorders: Amnesia, akathisia, balance disorder, cognitive disorder, disturbance in attention, dizziness postural, dizziness exertional, dysgeusia, hyperesthesia, hypoaesthesia, hypersomnia, memory impairment, mental impairment, migraine, neuropathy peripheral, paresthesia, sedation, slow speech, tremor, tunnel vision, wiith nerve paralysis.

Psychiatric disorders: Abnormal dreams, agitation, anger, anorgasmia, bruxism, confusional state, delusion, depression, disorientation, dysphoria, euphoric mood, hallucination, initial insomnia, libido decreased, libido increased, logorrhea, nervousness, nightmare, middle insomnia, mood swings, paranoia, restlessness, sleep talking, somnambulism, suicidal ideation, tension.

Reproductive System and Breast Disorders: Breast mass, breast tenderness, erectile dysfunction, menopausal symptoms.

Renal and Urinary Disorders: Bladder spasm, cystitis interstitial, dysuria, pollakiuria, urinary incontinence, urinary hesitation.

Respiratory, Thoracic and Mediastinal Disorders: Acute respiratory failure, cough, dyspnea, dry throat, hiccups, hypoxia, nasal discomfort, pharyngeal hypoaesthesia, rhinorrhea, yawning.

Skin and Subcutaneous Tissue Disorders: Acne, cold sweat, dry skin, ecchymosis, erythema, night sweats, onychoclasia, pain of skin, pruritus generalized, urticarial.

Vascular disorders: Flushing, hot flush, hypertension.

Post-Market Adverse Drug Reactions

In addition to adverse events reported from clinical trials, the following events have been identified during post-market use of BELBUCA. Because these reactions are reported voluntarily from a population of an unknown size, it is not always possible to reliably estimate their frequency.

Androgen deficiency: Chronic use of opioids may influence the hypothalamic-pituitary-gonadal axis, leading to androgen deficiency that may manifest as low libido, impotence, erectile dysfunction, amenorrhea, or infertility. The causal role of opioids in the clinical syndrome of hypogonadism is unknown because the various medical, physical, lifestyle, and psychological stressors that may influence gonadal hormone levels have not been adequately controlled for in studies conducted to date. Patients presenting with symptoms of androgen deficiency should undergo laboratory evaluation.

DRUG INTERACTIONS

Overview

Additive effects of other CNS Depressants (including benzodiazepines and alcohol):

The concomitant use of BELBUCA with other CNS depressants including sedatives/hypnotics, tricyclic antidepressants, general anesthetics, antipsychotics (e.g. phenothiazines), other opioids, antihistamines, benzodiazepines, centrally-active anti-emetics and alcohol can increase the risk of respiratory depression, profound sedation, hypotension, coma and death.

Patients receiving CNS depressants and BELBUCA should be monitored for signs of respiratory depression, sedation and hypotension. When combined therapy with any of the above medications is considered, the dose of one or both agents should be reduced (see **WARNINGS AND PRECAUTIONS, Neurologic- Interaction with other Central Nervous System depressants**).

Patients should also be warned that these combinations increase central nervous system depression and can make driving vehicles and operating machinery hazardous (see **WARNINGS AND PRECAUTIONS, Psychomotor Impairment**). Patients should be cautioned not to consume alcohol while using BELBUCA as it may increase the chance of experiencing dangerous side effects.

Drug-Drug Interactions

CYP 3A4 Enzyme Inhibitors:

Buprenorphine is primarily metabolized by glucuronidation and to a lesser extent by CYP3A4 enzyme. Concomitant treatment with CYP3A4 enzyme inhibitors (e.g., ritonavir, ketoconazole, itraconazole, troleandomycin, clarithromycin, nelfinavir, nefazodone, verapamil, diltiazem, amiodarone, amprenavir, fosamprenavir, aprepitant, fluconazole, erythromycin and grapefruit juice) may lead to elevated plasma concentrations with an increase in dose-related toxicity of buprenorphine including QTc prolongation and potentially fatal respiratory depression.

If co-administration of CYP3A4 enzyme inhibitors is necessary while a patient is treated with BELBUCA, patient should be monitored for signs of adverse events including opioid overdose and respiratory depression. Conversely, if the discontinuation of CYP3A4 inhibitors is necessary, patient should be monitored for signs of opioid withdrawal (see **WARNINGS AND PRECAUTIONS, Concomitant Use of CYP3A4 Inhibitors**).

CYP 3A4 Enzyme Inducers:

The interaction between buprenorphine and CYP3A4 enzyme inducers has not been studied. Co-administration of BELBUCA and CYP3A4 enzyme inducers (e.g., phenobarbital, carbamazepine, phenytoin, and rifampin) can decrease the plasma concentration of buprenorphine, potentially resulting in decreased efficacy or onset of a withdrawal syndrome in patients who have developed physical dependence to buprenorphine. If co-administration of a CYP3A4 inducer is necessary while a patient is treated with BELBUCA, patient should be monitored for signs of opioid withdrawal. In opposition, if the discontinuation of CYP3A4 inducers is necessary, patient should be monitored for the emergence of adverse events, including potential fatal respiratory depression. In both cases, dose adjustments should be considered until stable drug effects are achieved (see **WARNINGS AND PRECAUTIONS**).

QTc Interval-Prolonging Drugs:

The concomitant use of BELBUCA with other QTc interval-prolonging drugs should be avoided (See **WARNINGS AND PRECAUTIONS, Cardiovascular; ACTION AND CLINICAL PHARMACOLOGY, Cardiac Electrocardiography**). Drugs that have been associated with QT interval prolongation and/or torsade de pointes include, but are not limited to, the examples in the following list. Chemical/pharmacological classes are listed if some, although not necessarily all, class members have been implicated in QTc interval prolongation and/or torsade de pointes:

Class IA antiarrhythmics (e.g., quinidine, procainamide, disopyramide), Class III antiarrhythmics (e.g., amiodarone, sotalol, ibutilide, dronedarone), Class 1C antiarrhythmics (e.g., flecainide, propafenone), antipsychotics (e.g., chlorpromazine, pimozide, haloperidol, droperidol, ziprasidone, risperidone), antidepressants (e.g., fluoxetine, citalopram, venlafaxine, tricyclic/tetracyclic antidepressants [e.g., amitriptyline, imipramine, maprotiline]), opioids (e.g.,

methadone), macrolide antibiotics and analogues (e.g., erythromycin, clarithromycin, azithromycin, tacrolimus), quinolone antibiotics (e.g., moxifloxacin, levofloxacin, ciprofloxacin), pentamidine, antimalarials (e.g., quinine, chloroquine), azole antifungals (e.g., ketoconazole, fluconazole, voriconazole), domperidone, 5-hydroxytryptamine (5-HT)₃ receptor antagonists (e.g., ondansetron), tyrosine kinase inhibitors (e.g., sunitinib, nilotinib, ceritinib, vandetanib), arsenic trioxide, histone deacetylase inhibitors (e.g., vorinostat), beta-2 adrenoceptor agonists (e.g., salmeterol, formoterol).

Drugs that Affect Electrolytes:

The use of buprenorphine with drugs that can disrupt electrolyte levels should be avoided. Drugs that can disrupt electrolyte levels include, but are not limited to, the following: loop, thiazide, and related diuretics; laxatives and enemas; amphotericin B; high-dose corticosteroids; proton pump inhibitors.

The above lists of potentially interacting drugs are not comprehensive. Current information sources should be consulted for newly approved drugs that prolong the QTc interval or decrease electrolytes, as well as for older drugs for which these effects have recently been established.

Muscle relaxants:

Buprenorphine may enhance the neuromuscular blocking action of skeletal muscle relaxants and produce an increased degree of respiratory depression. Monitor patients receiving muscle relaxants and BELBUCA for signs of respiratory depression that may be greater than otherwise expected.

Anticholinergics:

The concomitant use of opioid analgesics, including buprenorphine, and anticholinergic drugs may increase the risk of urinary retention and/or severe constipation, which may lead to paralytic ileus. Monitor patients for signs of urinary retention or reduced gastric motility when BELBUCA is used concurrently with anticholinergic drugs.

Benzodiazepines:

There have been a number of reports regarding coma and death associated with the misuse and abuse of the combination of buprenorphine and benzodiazepines. In many, but not all of these cases, buprenorphine was misused by self-injection of crushed buprenorphine tablets. Preclinical studies have shown that the combination of benzodiazepines and buprenorphine altered the usual ceiling effect on buprenorphine-induced respiratory depression, making the respiratory effects of buprenorphine appear similar to those of full opioid agonists. Closely monitor patients with concurrent use of BELBUCA and benzodiazepines. Warn patients that it is extremely dangerous to self-administer benzodiazepines while taking BELBUCA, and warn patients to use benzodiazepines concurrently with BELBUCA only as directed by their physician.

Mixed Agonist/Antagonist and Partial Agonist Opioid Analgesics:

The concomitant use of mixed agonist/antagonist and partial agonist opioid (e.g. nalbuphine or pentazocine) may reduce the analgesic effect of BELBUCA and/or precipitate withdrawal symptoms; therefore the concomitant use should be avoided.

Antiretrovirals - Non-nucleoside reverse transcriptase inhibitors (NNRTIs):

The NNRTIs are metabolized principally by CYP3A4. Efavirenz, nevirapine, and etravirine are known CYP3A4 inducers; whereas delavirdine is a CYP3A4 inhibitor. Significant pharmacokinetics interactions between NNRTIs (e.g., efavirenz and delavirdine) and buprenorphine have been shown in clinical studies, but these pharmacokinetic interactions did not result in any significant pharmacodynamics effects. Therefore, patients who are on chronic BELBUCA treatment should have their dose monitored if NNRTIs are added to their treatment regimen.

Antiretrovirals - Protease inhibitors (PIs):

Studies have shown that some antiretroviral protease inhibitors (PIs) with CYP3A4 inhibitory activity (nelfinavir, lopinavir/ritonavir, ritonavir) have little effect on buprenorphine pharmacokinetic and no significant pharmacodynamic effects. Other PIs with CYP3A4 inhibitory activity (atazanavir and atazanavir/ritonavir) resulted in elevated levels of buprenorphine and norbuprenorphine, and patients in one study reported increased sedation. Symptoms of opioid excess have been found in post-marketing reports of patients receiving buprenorphine and atazanavir with and without ritonavir concomitantly. Monitor patients taking BELBUCA and atazanavir with and without ritonavir. Dose reduction of BELBUCA may be warranted.

Serotonergic Agents: Coadministration of buprenorphine with a serotonergic agent, such as a selective serotonin re-uptake inhibitor or a serotonin norepinephrine re-uptake inhibitor, may increase the risk of serotonin syndrome, a potentially life-threatening condition (see **WARNINGS AND PRECAUTIONS, Neurologic**).

Drug-Food Interactions:

BELBUCA adheres to the moist buccal mucosa and will completely dissolve after application, usually within 30 minutes. The film should not be manipulated with the tongue or finger(s) and eating food and drinking any liquids should be avoided until the film has dissolved (see **DOSAGE AND ADMINISTRATION**).

Drug-Herb Interactions:

Interactions with herbal products have not been established.

Drug-Laboratory Interactions:

Interactions with laboratory tests have not been established.

Drug-Lifestyle Interactions:

The concomitant use of alcohol should be avoided (see **WARNINGS AND PRECAUTIONS, General**).

DOSAGE AND ADMINISTRATION

All doses of opioids carry an inherent risk of fatal or non-fatal adverse events. This risk is increased with higher doses. For the management of chronic non-cancer, non-palliative pain, it is recommended that 90 morphine milligram equivalent of BELBUCA[®] (buprenorphine buccal soluble film) not be exceeded (see Table 4 for the initial BELBUCA dose based on prior opioid expressed as oral morphine sulfate equivalents). Each patient should be assessed for their risk prior to prescribing BELBUCA, as the likelihood of experiencing serious adverse events can depend upon the type of opioid, duration of treatment, level of pain as well as the patient's own level of tolerance. In addition, the level of pain should be assessed routinely to confirm the most appropriate dose and the need for further use of BELBUCA (see DOSAGE AND ADMINISTRATION - Adjustment or Reduction of Dosage).

BELBUCA should only be used in patients for whom alternative treatment options (e.g., non-opioid analgesics) are ineffective, or not tolerated, or would be otherwise inadequate to provide appropriate management of pain.

BELBUCA should only be prescribed by persons knowledgeable in the continuous administration of potent opioids, in the management of patients receiving potent opioids for treatment of pain, and in the detection and management of respiratory depression including the use of opioid antagonists.

BELBUCA must be applied only to the buccal mucosa every 12 hours. Improper use such as chewing or swallowing the BELBUCA film may result in lower peak concentrations and lower bioavailability/efficacy.

BELBUCA doses of 600 mcg, 750 mcg and 900 mcg are for opioid-experienced patients. Patients are considered opioid-experienced if they have been taking at least 30 mg of oral Morphine Sulfate Equivalent (MSE) daily for at least 4 weeks.

BELBUCA should not be used if the pouch seal is broken or if the buccal film is cut, damaged, or changed in any way. BELBUCA must not be cut.

Administration

First, the patient must use his tongue to wet the inside of his cheek or rinse his mouth with water to wet the area prior application of BELBUCA. BELBUCA should be applied immediately after removal from the individually sealed package. The entire BELBUCA film should be held with a clean, dry finger with the yellow side facing up. The yellow side of the BELBUCA should be placed against the inside of the cheek. BELBUCA film should be pressed and held in place for 5 seconds and then left on the inside of the cheek until fully dissolved.

BELBUCA adheres to the moist buccal mucosa and will completely dissolve after application, usually within 30 minutes. The film should not be manipulated with the tongue or finger(s) and eating food and drinking liquids should be avoided until the film has dissolved.

Proper administration technique should be demonstrated to the patient.

Recommended Dose and Dosage Adjustment

Initial dosing

BELBUCA doses must be individualized according to the response and tolerance of each patient and should be assessed at regular intervals. Proper optimization of doses scaled to the individual's pain should aim at the regular administration of the lowest dose of BELBUCA which provides pain relief.

BELBUCA should be taken at the determined dosage twice daily (every 12 hours) according to a fixed time schedule. **Single doses should not exceed 900 mcg of buprenorphine every 12 hours due to potential QTc interval prolongation. The maximum daily dose of BELBUCA is 1800 mcg.**

Physicians should consider prescribing not more than the appropriate amount of doses to achieve an adequate titration to the dose that controls the patient's pain.

Adults (over 18 years)

Patients not receiving opioids at the time of initiation of BELBUCA treatment (opioid-naïve)
Initiate treatment in opioid naïve patients with a 75 mcg film once daily or 75 mcg b.i.d (every 12 hours) if tolerated for at least 4 days, then increase dose to 150 mcg b.i.d (every 12 hours) for at least another 4 days (see Table 3). If pain is not adequately controlled, the subsequent dose increase should be based on individual titration, to a dose that provides adequate analgesia and minimized adverse reactions. The titration should proceed by incremental increase of no more than 150 mcg b.i.d (every 12 hours) for at least 4 days before the next 150 mcg b.i.d increment is implemented. Titration up to 450 mcg b.i.d (every 12 hours) were studied in opioid-naïve patients in clinical trials.

Table 3: Initial BELBUCA dose in Opioid-naïve patients

Initiate at 75 mcg (initiation dose) once daily or b.i.d (every 12 hours).
Increase to 150 mcg b.i.d (every 12 hours) no earlier than 4 days after initial dose.
Titrate by increments of 150 mcg b.i.d (every 12 hours) no earlier than every 4 days up to a dose that provides adequate analgesia and minimizes adverse reactions.
Maximum dose is 450 mcg b.i.d (every 12 hours).

Patient currently receiving other opioids (Opioid-experienced)

There is a potential for buprenorphine to precipitate withdrawal in patients who are already on opioid therapy. To reduce the risk of opioid withdrawal, patients should be tapered to at least 30 mg oral morphine sulfate equivalent (MSE) daily before beginning BELBUCA. The taper phase should be based on the patient's daily MSE dose prior to tapering. Tapering should not be overly aggressive and patients should be stabilised before initiating BELBUCA. During BELBUCA clinical trials, the taper phase (to at least 30 mg MSE per day) took up to 4 weeks.

Following analgesic taper, base BELBUCA starting dose on the patient's daily opioid dose prior to taper, as described in Table 4. Patients may require additional short-acting analgesics during the taper period and during titration.

BELBUCA may not provide adequate analgesia for patients requiring greater than 160 mg oral MSE per day. Consider the use of an alternate analgesic if necessary.

Table 4: Initial BELBUCA dose based on Prior Opioid Expressed as Oral Morphine Sulfate Equivalents

Prior Daily Dose of Opioid Analgesic Before Taper to 30 mg Oral MSE per day	Initial BELBUCA Dose
Less than 30 mg oral MSE	75 mcg once daily or every 12 hours
30 mg to 89 mg oral MSE	150 mcg every 12 hours
90 mg to 160 mg oral MSE	300 mcg every 12 hours
Greater than 160 mg oral MSE	Maximum dose is 450 mcg every 12 hours

BELBUCA doses of 600 mcg, 750 mcg, and 900 mcg are only for use following titration from lower doses of BELBUCA. Individual titration should proceed by incremental increase of no more than 150 mcg b.i.d for at least 4 days before the next 150 mcg b.i.d increment is implemented.

Conversion from Methadone to BELBUCA

Close monitoring is of particular importance when converting from methadone to other opioid agonists, including BELBUCA. The ratio between methadone and other opioid agonists may vary widely as a function of previous dose exposure. Methadone has a long half-life and can accumulate in the plasma. **Patients should be initiated on the lowest appropriate BELBUCA starting dose as indicated in Table 4, provided with adequate rescue medication, such as short-acting analgesics and titrated to a dose that achieves satisfactory pain relief with acceptable side effects. BELBUCA doses must be individualized and should be assessed at regular intervals.**

Titration and Maintenance of Therapy

The minimum titration interval of BELBUCA is 4 days, based on the pharmacokinetic profile and time to reach steady state plasma levels. Individual titration should proceed by incremental increase of no more than 150 mcg b.i.d (every 12 hours) for at least 4 days before the next 150 mcg b.i.d increment is implemented.

Proper optimization of doses scaled to the relief of the individual's pain should aim at administration of the lowest dose which will achieve the overall treatment goal of satisfactory pain relief with acceptable side effects. Dosage adjustments should be based on the patient's clinical response.

The maximum BELBUCA single dose is 900 mcg every 12 hours. The maximum daily dose of BELBUCA is 1800 mcg. The efficacy and safety of long-term administration of doses of BELBUCA above 900 mcg every 12 hours have not been studied.

Patients who experience breakthrough pain may require a dose increase of BELBUCA, or may need a rescue medication with an appropriate dose of an immediate-release analgesic. If the level of pain increases after dose stabilization, attempt to identify the source of increased pain while adjusting the BELBUCA dose to decrease the level of pain.

If unacceptable opioid-related adverse reactions are observed, the subsequent doses may be reduced. Adjust the dose to obtain an appropriate balance between management of pain and opioid-related adverse reactions.

Patients with Hepatic Impairment

BELBUCA has not been evaluated in patients with moderate and severe hepatic impairment.

Severe hepatic impairment: Consider reducing the starting dose and the titration dose by half compared to patients with normal liver function (e.g., from 150 mcg to 75 mcg), and monitor for signs and symptoms of toxicity or overdose caused by increased levels of buprenorphine (see **WARNINGS AND PRECAUTIONS**).

Mild and moderate hepatic impairment: Although no dose adjustment is necessary for patients with mild or moderate hepatic impairment, BELBUCA should be used with caution in these patients; patients should be monitored for signs and symptoms of toxicity or overdose caused by increased levels of buprenorphine.

Discontinuation of BELBUCA

Careful and regular monitoring are required to establish required maintenance of treatment. When the patient no longer requires therapy with BELBUCA, doses should be tapered gradually to prevent signs and symptoms of withdrawal in the dependent patient (see **WARNINGS AND PRECAUTIONS**).

Adjustment or Reduction of Dosage: Physical dependence with or without psychological dependence tends to occur with chronic administration of opioids, including BELBUCA. Withdrawal (abstinence) symptoms may occur following abrupt discontinuation of therapy. These symptoms may include body aches, diarrhea, gooseflesh, loss of appetite, nausea, nervousness or restlessness, runny nose, sneezing, tremors or shivering, stomach cramps, tachycardia, trouble with sleeping, unusual increase in sweating, palpitations, unexplained fever, weakness and yawning.

Following successful relief of severe pain, periodic attempts to reduce the opioid dose should be made. Smaller doses or complete discontinuation may become feasible due to a change in the patient's condition or mental state. Patients on prolonged therapy should be withdrawn gradually from the drug if it is no longer required for pain control. In patients who are appropriately treated with opioid analgesics and who undergo gradual withdrawal for the drug, these symptoms are usually mild (see **WARNINGS AND PRECAUTIONS**). Tapering should be individualized and carried out under medical supervision.

Patient should be informed that reducing and/or discontinuing opioids decreases their tolerance to these drugs. If treatment needs to be re-initiated, the patient must start at the lowest dose and titrate up to avoid overdose.

Missed Dose

If the patient forgets to take one or more doses, they should take the dose at the next scheduled time and in the normal amount. **They must not double the dose.**

Disposal

BELBUCA should be kept in a safe place, such as under lock and out of the sight and reach of children before, during and after use.

Unused or expired BELBUCA should be properly disposed of as soon as it is no longer needed to prevent accidental exposure to others, including children or pets. BELBUCA should not be shared with others and steps should be taken to protect it from theft or misuse. Patient should speak to their pharmacist about temporary storage options, if required, until the medication can be returned to the pharmacy for safe disposal.

BELBUCA should never be disposed of in household trash. Disposal via a pharmacy take back program is recommended.

OVERDOSAGE

For management of a suspected drug overdose, contact your regional Poison Control Centre.

Symptoms:

Symptoms of an overdose with BELBUCA[®] include respiratory depression, sedation, drowsiness, nausea, vomiting and marked miosis. Respiratory depression is not always present in cases of buprenorphine overdose. However, respiratory depression, including apnea, and cardiovascular collapse, has occurred in some cases of buprenorphine overdose but not always.

Treatment:

ECG monitoring is recommended. Cardiac arrest or arrhythmias will require advanced life support techniques.

Primary attention should be given to the establishment of adequate respiratory exchange through the provision of a patent airway and controlled or assisted ventilation. Oxygen, intravenous fluids, vasopressors, and other supportive measures should be employed as indicated.

Due to the extremely slow dissociation of buprenorphine from opioid receptors, naloxone may not be effective in reversing any respiratory depression produced by buprenorphine. Consequently, even high doses of naloxone, 10-35 mg/70kg, may be of limited value in the management of buprenorphine overdose. The onset of naloxone effect may be delayed by 30 minutes or more.

Because the duration of naloxone reversal would be expected to be less than the duration of action of buprenorphine from BELBUCA, carefully monitor the patient until spontaneous respiration is reliably re-established. Repeated doses of naloxone should be administered if necessary. Even in the face of improvement, continued medical monitoring is required for at least 24 hours because of the possibility of extended effects of buprenorphine.

In an individual physically dependent on opioids, administration of an opioid receptor antagonist may precipitate an acute withdrawal. The severity of the withdrawal will depend on the degree of physical dependence and the dose of the antagonist administered. If a decision is made to treat serious respiratory depression in the physically dependent patient with an opioid antagonist, administration of the antagonist should be done with care and by titration with smaller than usual doses of the antagonist.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Buprenorphine interacts with several opioid receptor subtypes: buprenorphine is a partial agonist at mu opioid receptors, an antagonist at kappa and delta opioid receptors, and a partial agonist at ORL-1 (nociceptin) receptors. The fundamental clinical actions of buprenorphine are thought to result from high affinity binding to, and slow dissociation from, mu opioid receptors. The contributions of kappa, delta and ORL-1 receptor actions to the analgesic profile of buprenorphine are unclear.

Pharmacodynamics

Effects on the Central Nervous System:

The principal action of therapeutic value of buprenorphine is analgesia and is thought to be due to buprenorphine binding with high affinity to opioid receptors on neurons in the brain and spinal cord. Buprenorphine may also cause sedation or somnolence via an action in the brain.

Buprenorphine produces mu opioid receptor-mediated respiratory depression by direct action on brainstem respiratory centers by reducing sensitivity of the brainstem to increases in carbon dioxide tension. Unlike other opioids, buprenorphine appears to exhibit a dose-ceiling effect on respiratory depression.

Buprenorphine causes miosis, even in total darkness, and little tolerance develops to this effect. Pinpoint pupils are a sign of opioid overdose but are not pathognomonic (e.g., pontine lesions of hemorrhagic or ischemic origins may produce similar findings). Marked mydriasis rather than miosis may be seen with worsening hypoxia in the setting of buprenorphine overdose.

Effects on the Gastrointestinal Tract and Other Smooth Muscle:

Buprenorphine causes a reduction in motility associated with an increase in smooth muscle tone in the antrum of the stomach and duodenum. Digestion of food in the small intestine is delayed and propulsive contractions are decreased. Propulsive peristaltic waves in the colon are decreased, while tone may be increased to the point of spasm resulting in constipation. Other opioid-induced effects may include a reduction in gastric, biliary and pancreatic secretions, spasm of the sphincter of Oddi, and transient elevations in serum amylase.

Effects on the Cardiovascular System:

Buprenorphine may produce release of histamine with or without associated peripheral vasodilation. Manifestations of histamine release and/or peripheral vasodilatation may include pruritus, flushing, red eyes, hyperhidrosis and/or orthostatic hypotension.

Effects on Cardiac Electrophysiology: Buprenorphine has been associated with concentration-dependent prolongation of the QTc interval in randomised, double-blind, placebo- and active-controlled ECG assessment studies in healthy subjects. During the open label titration phase of **BELBUCA** controlled pivotal studies (EN3409-307 and EN3409-308), 48 subjects experienced changes from baseline in their QTcF values in the range of 30 to 60 msec. No subject experienced any greater change. During the double-blind treatment phase, 13 subjects (2.7%) in the buprenorphine group and 6 subjects (1.3%) in the placebo group had QTcF values ≥ 450 msec.

Effects on the Endocrine System:

Chronic use of any opioid may influence the hypothalamic-pituitary-adrenal or -gonadal axes. Changes may include an increase in serum prolactin, and decreases in plasma cortisol and testosterone. Clinical signs and symptoms may be manifest as low libido, impotence, erectile dysfunction, amenorrhea, or infertility.

Effects on the Immune System:

Opioids have been shown to have a variety of effects on components of the immune system in *in vitro* and animal models. The clinical significance of these findings is unknown. Overall, the effects of opioids appear to be modestly immunosuppressive.

Pharmacokinetics

Absorption: Systemic exposure to buprenorphine (AUC_T; area under the plasma concentration versus time curve) from buprenorphine HCl buccal film was proportional to dose over the dose range studied (75 mcg to 1200 mcg), as shown in Table 5. The absolute bioavailability of buprenorphine in **BELBUCA** is approximately 50%.

Table 5: BELBUCA (buprenorphine) Pharmacokinetic Parameters Mean (\pm SD)

Regimen	Dosage (mcg)	Cmax (ng/mL)	AUC _{0-t} (ng·h/mL)	T _{max} * (hr)
Single dose	75	0.17 \pm 0.30	0.46 \pm 0.22	3.00 (1.50-4.05)
	300	0.47 \pm 0.47	2.04 \pm 0.68	2.50 (0.50-4.00)
	1200	1.43 \pm 0.45	9.59 \pm 2.92	3.00 (1.00-4.02)

* T_{max} values reported as median and range

Following multiple dose administration (60 to 240 mcg every 12 hours) of buprenorphine buccal film, apparent steady-state buprenorphine plasma concentrations were achieved prior to the 6th dose. Buprenorphine steady-state Cmax and AUC increased in a dose-proportional manner.

Systemic exposure to buprenorphine from **BELBUCA** film was reduced by 23-27% by the ingestion of liquids (cold, hot and room temperature water) during film administration; additionally coadministration with low pH liquid decreased buprenorphine exposure from **BELBUCA** by approximately 37%. The consumption of all liquids should be avoided until the buccal film has completely dissolved.

Distribution: Buprenorphine is approximately 96% bound to plasma proteins, primarily to alpha and beta globulin.

Metabolism: Buprenorphine undergoes both N-dealkylation to norbuprenorphine and glucuronidation. The N-dealkylation pathway is mediated primarily by CYP3A4. Norbuprenorphine, the major metabolite, can further undergo glucuronidation. Norbuprenorphine has been found to bind opioid receptors *in vitro*; however, it has not been studied clinically for opioid-like activity.

Excretion: A mass balance study of buprenorphine showed complete recovery of radiolabel in urine (30%) and feces (69%) collected up to 11 days after dosing. Almost all the dose was accounted for in terms of buprenorphine, norbuprenorphine, and two unidentified buprenorphine metabolites. In urine, most of buprenorphine and norbuprenorphine was conjugated (buprenorphine, 1% free and 9.4% conjugated; norbuprenorphine, 2.7% free and 11% conjugated). In feces, almost all of the buprenorphine and norbuprenorphine was free (buprenorphine, 33% free and 5% conjugated; norbuprenorphine, 21% free and 2% conjugated).

Based on multiple-dose studies performed with BELBUCA, the mean plasma elimination half-life of buprenorphine was 27.6±11.2 hours.

Special Populations and Conditions

Pediatrics: The pharmacokinetics of BELBUCA have not been studied in patients less than 18 years of age.

Geriatrics: Two population-PK clinical studies of BELBUCA did not identify any notable differences in pharmacokinetics in subjects aged above 65 compared to younger subjects. Other reported clinical experience with buprenorphine has not identified differences in responses between the elderly and younger patients. Although specific dose adjustments on the basis of advanced age are not required for pharmacokinetic reasons, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, concomitant disease or other drug therapy.

Gender: No differences in plasma buprenorphine concentrations were detected between males and females treated with BELBUCA.

Race: No differences in plasma buprenorphine concentrations were detected between races treated with BELBUCA.

Oral Mucositis: In a pharmacokinetic study in 6 cancer patients with Grade 3 mucositis, buprenorphine was absorbed more rapidly from BELBUCA resulting in a higher C_{max} (~80%) and larger AUC (~60%) compared to age- and gender-matched healthy control patients. BELBUCA should not be used in patients with known or suspected oral mucositis.

Hepatic Insufficiency: BELBUCA has not been evaluated in patients with hepatic impairment. The effects of hepatic impairment on the pharmacokinetics of buprenorphine were evaluated in a pharmacokinetic study. Buprenorphine is extensively metabolized in the liver and buprenorphine

plasma levels were found to be higher and the half-life was found to be longer in subjects with moderate and severe hepatic impairment, but not in subjects with mild hepatic impairment.

Based on these data, a dosage reduction in patients with severe hepatic impairment (i.e., Child-Pugh score above 9) is recommended. There is no need for dosage adjustment when using BELBUCA in patients with mild to moderate hepatic impairment (see **DOSAGE AND ADMINISTRATION**).

Renal Insufficiency: No studies in patients with renal impairment have been performed with BELBUCA. Independent studies have shown that buprenorphine pharmacokinetics were similar in adult patients with severe renal impairment compared to normal adults.

STORAGE AND STABILITY

Store BELBUCA between 15° and 30 °C.

SPECIAL HANDLING INSTRUCTIONS

BELBUCA[®] (buprenorphine buccal soluble film) should be kept in a safe place out of the sight and reach of children before, during and after use. **BELBUCA should not be used in front of children, since they may copy these actions.** Do not give to others. BELBUCA buccal soluble film should not be cut, damaged or changed in any way.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Film component

BELBUCA[®] is a buccal soluble film providing transmucosal delivery of buprenorphine hydrochloride. BELBUCA is a rectangular bi-layer, peppermint-flavored, buccal film with rounded corners, consisting of a white to off-white backing layer with strength identifier printed in black ink and a light yellow to yellow active mucoadhesive layer containing buprenorphine hydrochloride. The yellow side of the buccal film is applied to the inside of the cheek where it adheres to the moist buccal mucosa to deliver the drug as the film dissolves.

BELBUCA contains the following inactive ingredients: Carboxymethylcellulose sodium, citric acid anhydrous, hydroxypropylcellulose, hydroxyethylcellulose, methylparaben, monobasic sodium phosphate, peppermint oil, polycarbophil, propylene glycol, propylparaben, saccharin sodium, sodium benzoate, sodium hydroxide, titanium dioxide and vitamin E acetate, yellow iron oxide, purified water, Shellac and black iron oxide.

Availability of dosage forms

BELBUCA is available in 7 dosage strengths: 75 mcg, 150 mcg, 300 mcg, 450 mcg, 600 mcg, 750 mcg and 900 mcg of buprenorphine per film. BELBUCA buccal films are light yellow to yellow on one side and white to off-white on the other side and are printed with following distinguishable characteristics:

- 75 mcg buccal film: E0 in black ink.
- 150 mcg buccal film: E1 in black ink.
- 300 mcg buccal film: E3 in black ink.
- 450 mcg buccal film: E4 in black ink.
- 600 mcg buccal film: E6 in black ink.
- 750 mcg buccal film: E7 in black ink.
- 900 mcg buccal film: E9 in black ink.

BELBUCA is supplied in boxes of 60 individual child-resistant foil packages.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

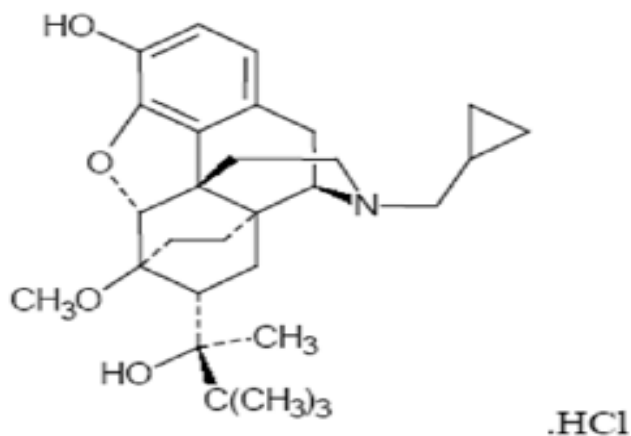
Drug Substance

Proper name: Buprenorphine hydrochloride

Chemical name: 6,14-Ethenomorphinan-7-methanol, 17-(cyclopropylmethyl)- α -(1,1-dimethylethyl)-4,5-epoxy-18,19-dihydro-3-hydroxy-6-methoxy- α -methyl-, hydrochloride, [5 α ,7 α (S)]

Molecular formula and molecular mass: C₂₉H₄₁NO₄.HCl 504.10

Structural formula:



Physicochemical properties: Buprenorphine is an opioid analgesic. White or off-white crystalline solid. Sparingly soluble in water, free soluble in methanol, soluble in alcohol, practically insoluble in cyclohexane.

CLINICAL TRIALS

The efficacy of BELBUCA[®] has been demonstrated in two (2) 12-week double-blind, randomised, controlled clinical trials in opioid-naïve and opioid-experienced patients with moderate-to-severe chronic low back pain (CLBP) using an 11-point numerical rating scale (NRS) pain score difference from baseline to week 12, as the primary efficacy variable.

Pivotal Clinical Trial Demographics, Designs, Protocols and Efficacy Results

Table 6: Summary of patient demographics and trial designs

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n = number)	Mean age (SD)	Gender (%)
EN3409-308	Phase 3, double-blind, placebo-controlled, enriched enrollment, multicenter, randomized, withdrawal	75, 150, 300, 450 mcg buprenorphine per film, applied to the buccal mucosa Q12h. 1. Screening phase (2 wk) 2. Open-label titration phase (8 wk including at least 2 wk at a stable “optimal” dose) 3. Double-blind treatment phase (12 wk) 4. F/U phase (2 wk)	Opioid-naïve patients E: 752 R: 462 S: 749 C: 350	49.9 (13.09)	F= 55 M=45
EN3409-307	Phase 3, double-blind, placebo-controlled, enriched enrollment, multicenter, randomized, withdrawal	150, 300, 450, 600, 750, 900 mcg buprenorphine per film, applied to the buccal mucosa, Q12h. 1. Screening phase (2 wk) 2. Analgesic taper phase (≤4 wk) 3. Open-label titration phase (≤8 wk including at least 2 wk at a stable “optimal” dose) 4. Double-blind treatment phase (12 wk) 5. F/U phase (2 wk)	Opioid-experienced patients E: 815 R: 511 S: 810 C: 353	53.3 (11.17)	F= 54.2 M= 45.8

E: Enrolled patients

R: Randomized patients

S: Patients used for Safety analysis

C: Completer patients

Protocols and Efficacy Results

Study 1 (EN3409-308)

A total of 749 opioid-naïve patients with chronic low back pain (CLBP) entered an open-label, dose-titration period for up to eight weeks. Patients initiated therapy with a single 75 mcg dose of BELBUCA on Day 1 and continued taking BELBUCA 75 mcg either once daily or every 12 hours thereafter for 4-8 days as tolerated. The dose was then increased to 150 mcg b.i.d. (every 12 hours), and patients could continue to dose escalate every 4-8 days in 150 mcg dose increments (every 12 hours) if the adverse effects were tolerable and the analgesic effects were not adequate. Patients who achieved adequate analgesia and tolerable adverse effects on no more than 450 mcg BELBUCA every 12 hours for at least 2 complete weeks before the end of week 8 were randomized to continue their titrated dose of BELBUCA or matching placebo.

Overall, the mean (SD) time to reach the optimal dose of buprenorphine in the open-label titration phase was 17.1 (7.77) days. Of the 230 patients randomized to BELBUCA, 77% completed the double blind randomized 12-week treatment period compared to 75% of the 232 patients randomized to placebo.

Rescue medication during the open-label titration period: One (1) to 2 tablets of acetaminophen were allowed to be used every 6 hours (Q6h), on a PRN basis, up to a maximum of 6 tablets (3,000 mg) per day in order to avoid liver injury.

Rescue medication during the double-blind period: During the first 2 weeks of double-blind treatment, patient were allowed up to 2 tablets per day of hydrocodone/acetaminophen 5/325 mg as supplemental analgesia to minimize opioid withdrawal symptoms in patients randomized to placebo. Thereafter, the supplemental analgesia was limited to 1 to 2 tablets of acetaminophen 500 mg per day.

Of the patients who were randomized, the mean pain (SD) Numeric Rating Scale (NRS) scores were 7.12 (1.06)/7.18 (1.05) prior to open-label titration, 2.82 (1.01)/2.79 (1.12) at the beginning of the double-blind period (baseline) and 3.76 (1.94)/4.39 (2.00) at week 12 of the double-blind 12 weeks period for BELBUCA/Placebo, respectively. The pain score difference of -0.67 for the primary efficacy endpoints (the change from double-blind baseline to week 12 in mean pain (SD) NRS score) was statistically significant favoring patients treated with BELBUCA compared with patients treated with placebo [0.93 (2.10) vs. 1.60 (2.13), respectively; P=0.0012]. Table 7 outlines the pain scores throughout the study. Treatment differences for the secondary endpoints were supportive of the treatment difference for the primary endpoints.

Table 7: Mean Numeric Rating Scale (NRS) pain scores and pain score differences at different stages of study EN3409-308 in opioid-naïve patients.

	Mean NRS pain scores (SD) prior to open-label titration phase	Mean NRS pain scores (SD) at randomization (baseline)	Mean NRS pain scores (SD) at week 12 of the double blind phase	Mean NRS pain score change from baseline to week 12 (SD)
BELBUCA	7.12 (1.06)	2.82 (1.01)	3.76 (1.94)	0.93 (2.10)
Placebo	7.18 (1.05)	2.79 (1.12)	4.39 (2.00)	1.60 (2.13)
Difference (BELBUCA-Placebo)	-0.06	0.03	-0.63	-0.67[▼] (p = 0.0012)

[▼]Treatment difference (BELBUCA - Placebo) for the primary endpoint is calculated using PROC MIANALYZE by combining results from ANCOVA model (Least Square Mean Difference), performed with change from baseline as the dependent variable, treatment as a fixed effect and screen and baseline value as covariates from 10 imputed datasets.

Study 2 (EN3409-307)

Eight hundred and ten (810) opioid-experienced patients on chronic opioid therapy (total daily dose 30-160 mg MSE) entered an open-label, dose-titration period with BELBUCA for up to 8 weeks, following taper of their prior opioids daily dose to 30 mg oral MSE daily. Patients were initiated with BELBUCA 150 mcg every 12 hours if they were on 30 to 89 mg oral MSE daily prior to taper and 300 mcg every 12 hours if they were on 90 to 160 mg oral MSE daily prior to taper. If a patient tolerated the adverse events and the analgesic effects were not adequate, the dose was increased in increments of 150 mcg every 12 hours after 4-8 days. Patients who achieved adequate analgesia and tolerable adverse effects on no more than 900 mcg BELBUCA every 12 hours for at least 2 complete weeks before the end of week 8 were randomized to continue their titrated dose of BELBUCA or matching placebo. Eighty-one percent (81%) of patients treated with BELBUCA and 57% of patients treated with placebo completed the double blind randomized 12-week treatment period.

Rescue medication during the open-label titration period: Patients were permitted to take up to 4 doses per day (1 or 2 tablets per dose of hydrocodone/acetaminophen 5/325 mg Q6h) as a PRN analgesic rescue for a maximum of 4 doses (8 tablets) per day.

Rescue medication during the double-blind period: Patients were permitted to take up to 2 doses per day of hydrocodone/acetaminophen (1 or 2 tablets of 5/325 mg per dose) for the first 2 weeks to minimize opioid withdrawal symptoms in patients randomized to placebo. After the first 2 weeks, patients were permitted to take only 1 dose per day of the rescue medication (the dose could be 1 or 2 tablets of 5/325 mg).

Of the patients who were able to be randomized in the double-blind period, the mean pain (SD) NRS scores were 6.79 (1.28)/6.64 (1.32) prior to open-label titration, 2.91 (0.99)/2.84 (1.05) at the beginning of the double-blind period (baseline) and 3.80 (1.73)/4.75 (1.78) at week 12 of the double-blind period for BELBUCA and placebo buccal film, respectively. The pain score difference of -0.98 for the primary efficacy endpoints (the change from baseline to week 12 in mean pain (SD) NRS score) was statistically significant in favor of patients treated with BELBUCA compared with patients treated with placebo [0.92 (1.81) vs. 1.90 (1.84),

respectively; P<0.00001]. Table 8 outlines the pain scores throughout the study. Treatment differences for the secondary endpoints were supportive of the treatment difference for the primary endpoints.

Table 8: Mean Numeric Rating Scale (NRS) pain scores and pain score differences at different stages of study EN3409-307 in opioid experienced patients.

	Mean NRS pain scores (SD) prior to open-label titration phase	Mean NRS pain scores (SD) at randomization (baseline)	Mean NRS pain scores (SD) at week 12 of the double blind phase	Mean NRS pain score change from baseline to week 12 (SD)
BELBUCA	6.79 (1.28)	2.91 (0.99)	3.80 (1.73)	0.92 (1.81)
Placebo	6.64 (1.32)	2.84 (1.05)	4.75 (1.78)	1.90 (1.84)
Difference (BELBUCA-Placebo)	0.15	0.07	-0.95	-0.98[▼] (P<0.00001)

[▼]Treatment difference (BELBUCA - Placebo) for the primary endpoint is calculated using PROC MIANALYZE by combining results from ANCOVA model (Least Square Mean Difference), performed with change from baseline as the dependent variable, treatment as a fixed effect and screen and baseline value as covariates from 10 imputed datasets. It is also adjusted for biases using the CHW/LH method.

DETAILED PHARMACOLOGY

Buprenorphine binds to μ -opioid, κ -opioid, δ -opioid, and nociceptin (Opioid Receptor-Like, [ORL-1]) receptors. Buprenorphine acts as a μ -opioid receptor partial agonist and a κ -opioid receptor antagonist. The binding affinity order of buprenorphine for opioid receptors is $\mu > \kappa > \delta$. Buprenorphine has a slow dissociation rate from the μ opioid receptor, which gives rise to its prolonged suppression of opioid withdrawal and blockage of exogenous opioids. Because of its partial agonist activity at receptors and its long half-life, buprenorphine has proven to be an excellent alternative to methadone for either maintenance therapy or detoxification of the opioid addict.

TOXICOLOGY

BELBUCA[®] has been shown to have differences in bioavailability compared to other buprenorphine-containing sublingual products. The exposure multiples listed below are based on body surface area comparisons (mg/m²) between animals and adult humans; all safety multiples are referenced to the maximal recommended human daily dose of BELBUCA (1.8 mg).

Carcinogenicity

Carcinogenicity studies of buprenorphine were conducted in Sprague-Dawley rats and CD-1 mice. Buprenorphine was administered in the diet to rats at doses of 0.6, 5.5, and 56 mg/kg/day for 27 months (estimated exposure multiples approximately 3-, 29- and 299- times the maximum recommended human dose (MRHD) of buccal Belbuca of 1.8 mg on a mg/m² basis, respectively). Statistically significant dose-related increases in testicular interstitial (Leydig's)

cell tumors occurred. In an 86-week study in CD-1 mice, buprenorphine was not carcinogenic at dietary doses up to 100 mg/kg/day (estimated exposure multiple approximately 267 times the MRHD).

Mutagenicity

Buprenorphine was studied in a series of tests utilizing gene, chromosome, and DNA interactions in both prokaryotic and eukaryotic systems. Results were negative in yeast (*S. cerevisiae*) for recombinant, gene convertant, or forward mutations; negative in *Bacillus subtilis* “rec” assay, negative for clastogenicity in CHO cells, Chinese hamster bone marrow and spermatogonia cells, and negative in the mouse lymphoma L5178Y assay.

Results were equivocal in the Ames test: negative in studies in two laboratories, but positive for frame shift mutation at a high dose (5 mg/plate) in a third study. Results were positive in the Green-Tweets (*E. coli*) survival test, positive in a DNA synthesis inhibition (DSI) test with testicular tissue from mice, for both *in vivo* and *in vitro* incorporation of [³H]thymidine, and positive in unscheduled DNA synthesis (UDS) test using testicular cells from mice.

Impairment of fertility

Reproduction studies of buprenorphine in rats demonstrated no evidence of impaired fertility at daily oral doses up to 80 mg/kg/day (estimated exposure multiple approximately 427 times the MRHD) or up to 5 mg/kg/day IM or SC (estimated exposure multiple approximately 27 times the MRHD).

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READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PATIENT MEDICATION INFORMATION

^NBELBUCA[®]

Buprenorphine buccal soluble film

Read this carefully before you start taking **BELBUCA** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **BELBUCA**.

Serious Warnings and Precautions

- **Even if you take BELBUCA as prescribed you are at risk for opioid addiction, abuse and misuse that can lead to overdose and death. To understand your risk of opioid addiction, abuse, and misuse, you should speak to your prescriber (e.g., doctor).**
- **Life-threatening breathing problems can happen while taking BELBUCA, especially if not taken as directed. Babies are at risk of life-threatening breathing problems if their mothers take opioids while pregnant or nursing. You will be at significant risk for overdose and death if you misuse or abuse BELBUCA by snorting or injecting the active ingredient.**
- **Never give anyone your BELBUCA. They could die from taking it. If a person has not been prescribed BELBUCA, taking even one dose can cause a fatal overdose. This is especially true for children. Selling or giving away this medicine is against the law.**
- **If you took BELBUCA while you were pregnant, whether for short or long periods of time or in small or large doses, your baby can suffer life-threatening withdrawal symptoms after birth. This can occur in the days after birth and for up to 4 weeks after delivery. If your baby has any of the following symptoms:**
 - **has changes in their breathing (such as weak, difficult or fast breathing)**
 - **is unusually difficult to comfort**
 - **has tremors (shakiness)**
 - **has increased stools, sneezing, yawning, vomiting, or fever****Seek immediate medical help for your baby**
- **Taking BELBUCA with other opioid medicines, benzodiazepines, alcohol, or other central nervous system depressants (including street drugs) can cause severe drowsiness, decreased awareness, breathing problems, coma, and death.**
- **Keep BELBUCA in a safe place away from children. Accidental use by a child is a medical emergency and may result in death. Never take your medicine in front of children as they will want to copy you. If a child accidentally comes in contact with BELBUCA, get emergency help right away.**

What is BELBUCA used for?

BELBUCA is used for the long-term management of pain, when:

- the pain is severe enough to require daily, around-the-clock pain medication
- the doctor determines that other treatment options are not able to effectively treat your pain

BELBUCA is NOT used (“as needed”) to treat pain that you only have once in a while.

How does BELBUCA work?

BELBUCA contains buprenorphine, a pain medication belonging to the class of medicines known as opioids which includes codeine, fentanyl, morphine and oxycodone. It relieves pain by acting on specific nerve cells of the spinal cord and brain.

What are the ingredients in BELBUCA?

Medicinal ingredient: Buprenorphine hydrochloride

Non-medicinal ingredients: Carboxymethylcellulose sodium, citric acid anhydrous, hydroxypropylcellulose, hydroxyethylcellulose, methylparaben, monobasic sodium phosphate, peppermint oil, polycarbophil, propylene glycol, propylparaben, saccharin sodium, sodium benzoate, sodium hydroxide, titanium dioxide, vitamin E acetate, yellow iron oxide, purified water and black ink (shellac, black iron oxide).

BELBUCA comes in the following dosage forms:

Buccal soluble films: 75 mcg, 150 mcg, 300 mcg, 450 mcg, 600 mcg, 750 mcg and 900 mcg.

Do not use BELBUCA if:

- your doctor did not prescribe it for you
- you are allergic to buprenorphine hydrochloride, other opioids, or any of the other ingredients in **BELBUCA**
- your pain is mild
- your pain comes and goes or only lasts for a short time, even if it is severe
- you have acute pain, including after an out-patient or day surgery
- you have severe asthma, trouble breathing, or any other lung problems
- you need pain relief after surgery or in cases where your pain varies a lot
- you have appendicitis or a problem with your pancreas called pancreatitis
- you are going to have a planned surgery
- you have a condition where the small bowel does not work properly (paralytic ileus) or you have severe pain in your abdomen
- you have a head injury
- if you are at risk for seizures
- you have CNS depression (reduced functioning of your brain and spinal cord)
- you suffer from alcoholism, including symptoms of alcohol withdrawal like confusion and seizures

- you take a type of medication called monoamine oxidase inhibitors or if you took them within the last 14 days
- you have a painful sore on the inside of the cheek
- you are being treated for narcotic withdrawal or dependence
- you are pregnant or plan to become pregnant, breast-feeding, or in labour
- you have myasthenia gravis, a condition where you have abnormal weakness in certain muscles
- you are under 18 years of age.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take BELBUCA. Talk about any health conditions or problems you may have, including if:

- you have a history of illicit or prescription drug or alcohol abuse
- you have severe kidney, liver, or lung disease
- you have heart disease
- you have problems with your thyroid, adrenal or prostate gland
- you have low blood pressure or are at risk of having low blood pressure
- you are going to have, or recently had, a planned surgery
- you have past or current depression
- you, or an immediate family member, have a heart rhythm problem (called Long QT syndrome)
- you suffer from chronic or severe constipation
- suffer from migraines

Other warnings you should know about:

Opioid dependence and addiction: There are important differences between physical dependence and addiction. It is important that you talk to your doctor if you have questions or concerns about abuse, addiction or physical dependence.

Pregnancy, nursing, labour and delivery: Do not use **BELBUCA** while pregnant, nursing, during labour or delivery. Opioids can be transferred to your baby through breast milk, or while still in the womb. **BELBUCA** can then cause life-threatening breathing problems in your unborn baby or nursing infant.

Heart rhythm disorder:

Buprenorphine, the active ingredient in **BELBUCA**, can cause a heart rhythm disorder. This disorder is called Long QT Syndrome. You may have no symptoms or you may:

- feel dizzy
- have chest pain or discomfort
- have a rapid, fluttering or pounding heart
- faint
- have seizures.

Tell your doctor immediately if you have these symptoms. If you continue to have these symptoms, you could develop a more serious heart rhythm problem that could lead to death.

Driving and using machines: Before you do tasks which may require special attention, you should wait until you know how you react to **BELBUCA**. **BELBUCA** can cause:

- drowsiness
- dizziness or
- light headedness

This can usually occur after you take your first dose and when your dose is increased.

Disorder of the adrenal gland: You may develop a disorder of the adrenal gland called adrenal insufficiency. This means that your adrenal gland is not making enough of certain hormones.

You may experience symptoms such as:

- nausea, vomiting
- feeling tired, weak or dizzy
- decreased appetite

You may be more likely to have problems with your adrenal gland if you have been taking opioids for longer than one month. Your doctor may do tests, give you another medication, and slowly take you off **BELBUCA**.

Serotonin syndrome: **BELBUCA** can cause serotonin syndrome, a rare but potentially life-threatening condition. It can cause serious changes in how your brain, muscles and digestive system work. You may develop Serotonin Syndrome if you take **BELBUCA** with certain anti-depressants or migraine medications.

Serotonin syndrome symptoms include:

- fever, sweating, shivering, diarrhea, nausea, vomiting;
- muscle shakes, jerks, twitches or stiffness, overactive reflexes, loss of coordination;
- fast heartbeat, changes in blood pressure;
- confusion, agitation, restlessness, hallucinations, mood changes, unconsciousness, and coma.

Sexual Function/Reproduction: Long term use of opioids may lead to a decrease in sex hormone levels. It may also lead to low libido (desire to have sex), erectile dysfunction or being infertile.

Monitoring:

Your doctor will monitor you while you are taking **BELBUCA**. The monitoring will occur:

- to determine if you are abusing or misusing **BELBUCA**
- to determine if you are at risk of overdose or serious breathing troubles
- to determine if you are developing low blood pressure
- if you already have seizures
- if you are taking certain other drugs while taking **BELBUCA**
- if you have problems with the ducts in your liver or pancreas

Your doctor will decide how often to monitor you and whether your dose needs to be adjusted.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with BELBUCA:

- Alcohol, including prescription and non-prescription medications containing alcohol. Avoid alcohol while taking **BELBUCA**. It can lead to:
 - drowsiness
 - depressed breathing
 - unusually slow or weak breathing
 - serious side effects
 - a fatal overdose
- other sedative drugs which may enhance the drowsiness caused by **BELBUCA**
- other opioid analgesics (for pain)
- certain drugs to treat seizures
- certain heart drugs
- certain cancer drugs
- diuretic drugs (to help your kidneys)
- laxative drugs and enemas
- high-dose steroids
- drugs used to help your muscles relax
- general anesthetics (used during surgery)
- drugs used to help you sleep or to reduce anxiety
- antidepressants (for depression and mood disorders). Do not take **BELBUCA** with monoamine oxidase (MAO) inhibitors or if you have taken MAO inhibitors in the last 14 days before treatment with **BELBUCA**
- drugs used to treat serious mental or emotional disorders, such as schizophrenia
- antihistamines (for allergies)
- anti-emetics (for prevention of vomiting)
- drugs used to treat muscle spasms and back pain
- warfarin and other coumarin anticoagulants (for prevention or treatment of blood clots)
- anti-retroviral drugs (used to treat certain viral infections, such as HIV/AIDS)
- anti-fungal drugs (used to treat fungal infections)
- antibiotic drugs (used to treat bacterial infections)

- grapefruit juice
- St. John's Wort

Taking **BELBUCA** with some of the drugs listed above can have serious side effects such as:

- severe breathing problems
- low blood pressure
- coma
- feeling very sedated
- death

Only take drugs that your doctor knows about and that have been prescribed for you.

How to take BELBUCA:

- **BELBUCA** is an oral adhesive film that you place on the inside of your cheek.
- Use **BELBUCA** only for the condition for which it was prescribed.
- Tell your doctor if your pain increases or if you have any new issues after starting **BELBUCA**.
- Contact your doctor or pharmacist if you have any questions about how to apply **BELBUCA**.

Usual Adult Dose:

- Take **BELBUCA** as prescribed by your doctor. Your doctor will determine the best dose for you:
 - If you have not taken opioids before, you will start with the 75 mcg dose.
 - If you are already taking opioids, your doctor will adjust the dose of your other opioids before you start taking **BELBUCA**.
 - If you have severe liver disease, you may be given a lower starting dose.
- The maximum daily dose of **BELBUCA** is 1800 mcg.
- Do not increase or decrease your dose or stop taking **BELBUCA** without talking to your doctor.
- Taking higher doses can lead to more side effects and greater chance of overdose.
- Apply **BELBUCA** every twelve (12) hours (morning and evening) at the same times each day.
- After the film has stuck to your cheek, don't eat or drink until the film is dissolved. This may take 30 minutes.

Keep the following points in mind when you are using BELBUCA:

- Only open the pouch when you are ready to use it.
- Open the pouch very carefully to avoid damaging the film.
- Avoid cutting, tearing, chewing or swallowing the film.
- Only use the film if the pouch seal is unbroken and if the film is undamaged or unchanged in any way.
- Refer to the Questions and Answers section further down in this leaflet if you have difficulty:
 - opening the pouch or
 - applying **BELBUCA** to the inside of your cheek.

Step 1: How to open the BELBUCA pouch

Each film is sealed in its own protective pouch.

- a) Hold the pouch as illustrated below (Figure 1).
- b) Fold along the dotted line at the top of the pouch. This will reveal the notch on the upper right hand corner to make the next step easier.

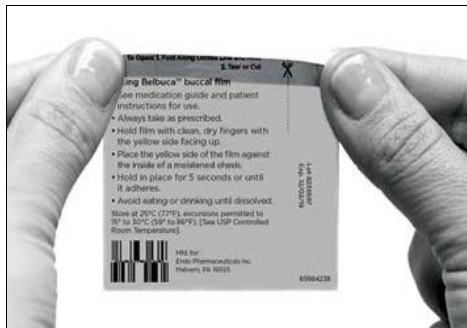


Figure 1



Figure 2

- c) Keep the top folded. Tear down at the notch in the direction of the scissors on the dotted line, either toward you or away from you. Tear all the way to the bottom (Figure 2). Use scissors to cut open the pouch if you have trouble tearing it. Be careful when tearing or cutting the pouch to avoid cutting and damaging the film.

Step 2: Applying the BELBUCA film

- a) Have a glass of water ready before you remove the film from the pouch. This will help you with step 2e) below.
- b) Hold the pouch open with one hand. Ensure the white side of the film is facing up. Insert your dry and clean forefinger into the pouch and place it on the white side of the film; then slowly pull it out. Try not to touch the yellow side of the film.
- c) When the film is half way out of the pouch, keep your forefinger on the film. Turn the pouch over with the other hand so the yellow side is facing up. The yellow side of the film will now be facing you.
- d) Do not use any objects to try to remove the film from the pouch. **Do not cut or tear the film.**

- e) Before applying the film:
- i. Rinse your mouth with water to moisten the area, especially if you have recently eaten or drank something other than water OR
 - ii. Use your tongue to wet the inside of your cheek.

- f) Hold the film with a clean, dry finger with the yellow side facing up (Figure 3).



Figure 3

- g) Using your finger, place the yellow side of the film against the inside of the moistened cheek. Avoid placing the film under your tongue. **Press and hold** the film in place for **5 seconds** (Figure 4) and then take your finger away.

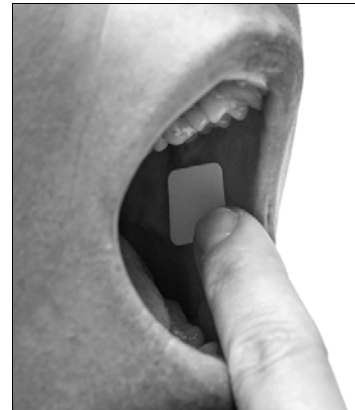


Figure 4

- h) The film will stick to the inside of your cheek (Figure 5).

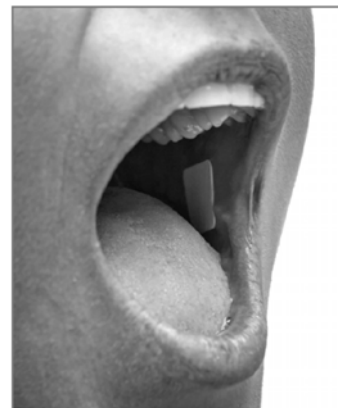


Figure 5

- i) Leave the film in place until it has completely dissolved – usually within 30 minutes after you apply it.
 - Avoid eating or drinking until it has dissolved.
 - Avoid touching or moving the film with your tongue or finger.
 - **Do not chew or swallow the film.**

Questions and Answers about using the BELBUCA film:

1. *Is it safe to touch the yellow side of the **BELBUCA** film?*
2. When using **BELBUCA**, your finger should not come in contact with the yellow side of film. If this happens, immediately turn the film over to make sure you only touch the white side. *What if I can't get the **BELBUCA** film out of the pouch?*
Cut along the top or bottom of the pouch. Try not to cut or damage the film. You can then peel back the pouch to access the film.
3. *What should I do if I cut or damage the **BELBUCA** film?*
Do not apply **BELBUCA** if the film is cut or damaged. If you cut or damage the film, place the damaged film back in its pouch and keep it in a safe place until it can be returned to the pharmacy for disposal.
4. *Can I wet my finger to pick up the **BELBUCA** film?*
Do not wet your finger to pick up the film. It will affect the way it works to relieve your pain. Always hold the film with clean, dry fingers with the yellow side facing up.
5. *Is there a specific place I should put the **BELBUCA** film in my mouth – deep, low, high or in the middle of my cheek?*
6. You can choose where to place the film on the inside of your cheek: deep, high, low or in the middle. Just make sure that the inside of your cheek is moistened. *What should I do if I swallow the **BELBUCA** film?*
If you swallow your film, wait for 12 hours before applying another film. You may use acetaminophen to help with your pain, if necessary. Call your doctor or pharmacist with any further questions or concerns.
7. *What should I do if the **BELBUCA** film folds over while it is stuck to my cheek?*
Remove the film if it folds and does not stick to your cheek. Wait for 12 hours before applying another film. You may use acetaminophen to help with your pain, if necessary. Call your doctor or pharmacist with any further questions or concerns.
8. *The **BELBUCA** film is moving around in my mouth – what should I do?*
If the film moves, hold it in place for 5 seconds on your cheek by using your tongue or a dry, clean forefinger. If the film does not stick to your cheek, remove it and wait for 12 hours before applying another film. You may use acetaminophen to help with your pain, if necessary. Call your doctor or pharmacist with any further questions or concerns.

Stopping your Medication:

You should not stop taking **BELBUCA** all at once if you have been taking it for more than a few days.

Your doctor will monitor and guide you on how to slowly stop taking **BELBUCA**. You should do it slowly to avoid uncomfortable symptoms such as having:

- body aches
- diarrhea
- goosebumps
- loss of appetite
- nausea
- feeling nervous or restless
- runny nose
- sneezing
- tremors or shivering
- stomach cramps
- rapid heart rate (tachycardia)
- having trouble with sleeping
- an unusual increase in sweating
- heart palpitations
- an unexplained fever
- weakness
- yawning.

By reducing or stopping your opioid treatment, your body will become less used to opioids. If you start treatment again, you will need to start at the lowest dose. You may overdose if you restart at the last dose you took before you slowly stopped taking **BELBUCA**.

Refilling Prescriptions for BELBUCA:

A new written prescription is required from your doctor each time you need more **BELBUCA**. Therefore, it is important that you contact your doctor before your current supply runs out.

Only obtain prescriptions for this medicine from the doctor in charge of your treatment. Do not seek prescriptions from other doctors unless you switch to another doctor for your pain management.

Overdose:

If you think you have taken too much **BELBUCA**, contact your healthcare professional, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Signs of overdose may include:

- unusually slow or weak breathing
- dizziness
- confusion
- extreme drowsiness
- tiredness
- nausea
- vomiting
- narrowed pupils

Missed Dose:

It is important that you do not miss any doses. If you miss a dose, take your next dose at your usual time. Do not take two doses at once. If you miss several doses in a row, talk to your doctor before restarting your medication.

What are possible side effects from using BELBUCA?

These are not all the possible side effects you may feel when taking **BELBUCA**. If you experience any side effects not listed here, contact your healthcare professional.

Side effects may include:

- Nausea
- Constipation
- Headache
- Dizziness
- Diarrhea
- Vomiting
- Sleepiness
- Tiredness
- Less appetite
- Muscle cramps
- Itching
- Sweating
- Dry mouth
- Low sex drive, impotence (erectile dysfunction), infertility

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
COMMON			
Fast, Slow or Irregular Heartbeat: heart palpitations, dizziness, chest pain or discomfort, rapid, fluttering or pounding heart, fainting, seizures.		√	
RARE			
Overdose: hallucinations, confusion, inability to walk normally, slow or weak breathing, extreme sleepiness, sedation, or dizziness, floppy muscles/low muscle tone, cold and clammy skin			√
Respiratory Depression: slow, shallow or weak breathing			√
Allergic Reaction: rash, hives, swelling of the face, lips, tongue or throat, difficulty swallowing or breathing			√
Bowel Blockage (impaction): abdominal pain, severe constipation, nausea			√
Withdrawal: nausea, vomiting, diarrhea, anxiety, shivering, cold and clammy skin, body aches, loss of appetite, sweating		√	
Low Blood Pressure: dizziness, fainting, light-headedness	√		
Jaundice: your skin or the white part of your eyes look yellow		√	
Serotonin Syndrome: agitation or restlessness, loss of muscle control or muscle twitching, tremor diarrhea			√

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

Reporting Side Effects

We encourage you to report serious or unexpected side effects to Health Canada. The information is used to check for new safety concerns about health products. As a consumer, your report contributes to the safe use of health products for everyone.

3 ways to report:

- Online at MedEffect: <https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html>
- By calling 1-866-234-2345 (toll-free);
- By completing a Consumer Side Effect Reporting Form and sending it by:
 - Fax to 1-866-678-6789 (toll-free), or
 - Mail to: Canada Vigilance Program
Health Canada, Postal Locator 1908C
Ottawa, ON
K1A 0K9

Postage paid labels and the Consumer Side Effect Reporting Form are available at MedEffect (<https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html>).

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

Storage:

- Keep unused or expired **BELBUCA** in a secure place to prevent theft, misuse or accidental exposure.
- Store between 15° and 30 °C. Keep in a dry place.
- Keep **BELBUCA** in its protective pouch until you are ready to use it.
- **Keep BELBUCA under lock and out of sight and reach of children and pets.**
- **Never take medicine in front of small children as they will want to copy you. Accidental ingestion by a child is dangerous and may result in death. If a child accidentally takes BELBUCA, get emergency help right away.**
- **Expired or unused BELBUCA should never be thrown into the household trash, where children and pets may find it.** It should be returned to a pharmacy for proper disposal.

If you want more information about BELBUCA:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website (<https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html>); the manufacturer's website (www.purdue.ca), or by calling 1-800-387-4501.

This leaflet was prepared by Purdue Pharma.

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